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Straightforward four-component access to spiroindolines†

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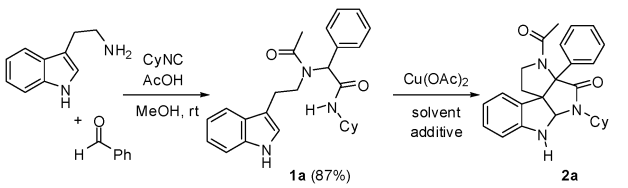
Spiroindolines could be synthesized *via* a very convenient one-pot procedure combining a Ugi coupling and a new copper-catalyzed oxidative process at a peptidyl position. Due to the nature of the first step, this method offers a straightforward access to complex alkaloids with four points of molecular diversity.

In the search for novel pharmacologic lead compounds, using molecular frameworks that resemble natural products with known biological activity is a good place to start.[1] Given the structural complexity and diversity of natural products, the construction of libraries of new compounds inspired by the structures of known natural products might be a complicated task that slows down new drug development.[1] Spiroindolenines and spiroindolines[2] are privileged motifs frequently encountered within a large family of alkaloids that includes communesines,[2,3] perophoramidines,[2,4] *etc*. Members of this alkaloid family display pronounced cytotoxicity and insecticidal activity.[1–4] Over the last decade, enormous efforts have been devoted to the development of novel and practical synthetic strategies for the construction of this molecular motif.[5,6]

Based on our interest in radical chemistry coupled with multicomponent processes,[7] we recently reported a Mn(III) triggered oxidative coupling of malonates with various Ugi adducts.[8] Although impressive, these transformations were hampered by the use of manganese salts in large excess. Wishing to identify suitable Ugi adducts that could be adapted to catalytic oxidative couplings, we turned our attention towards the indole core as an efficient radical trapping moiety.[9] According to the regioselectivity of the radical attack on the indole, this strategy could give us access to spiroindoline or indolenine derivatives as final targets. Aerobic oxidations constitute a vibrant research area,[10] and we found the multicomponent preparation of complex natural product-like structures under such conditions to be very appealing.

Table 1 Alkyne radical cyclization of xanthate substituted Ugi adducts



Entry	Equiv. of $Cu(OAc)_2$	Solvent (time, temp)	Additive	Yield (%)
1	1	MeCN (5 d, rt)	—	5
2	1	MeCN (2.5 h, reflux)	DBU	11
3	1	CF_3CH_2OH (6 d, reflux)	DBU	N. R.
4	1	MeOH (4 d, reflux)	DBU	25
5	1	THF (6 h, reflux)	DBU	77
6	0.5	THF (6 h, reflux)	DBU	59
7	0.3	THF (6 h, reflux)	DBU	49
8	0.3	PhF (16 h, reflux)	DBU	46

To evaluate the feasibility of the reaction, we prepared the Ugi adduct **1a** using benzaldehyde and tryptamine as the amine partner (Table 1). First trials were performed using one equivalent of copper acetate in acetonitrile in the absence of a base. The desired cyclized product was isolated in 5% yield (Table 1, entry 1). Encouraged by this observation, we surmised that the oxidation of the enolate should be much more efficient. Therefore, we repeated the reaction adding one equivalent of DBU in the mixture and achieved a slight improvement in the yield (Table 1, entry 2). A screening of the solvent (Table 2, entries 3–5) showed that THF was the best choice, as the product was isolated in 77% yield (Table 1, entry 5). Even if the product could still be obtained using either 0.5 or 0.3 equivalents of copper salt (Table 1, entries 6–8), the latter conditions were preferred due to their higher efficiency.

The presence of an aliphatic substituent at the peptidic position—by use of an aliphatic aldehyde in the former Ugi coupling—inhibited the reaction and no cyclization occurred (Table 2, entry 1). This result is consistent with a lower acidity of the proton, and suggested that in this reaction, the NH

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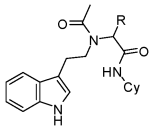
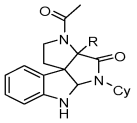
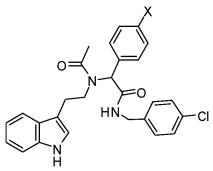
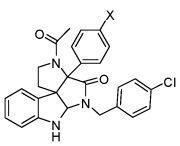
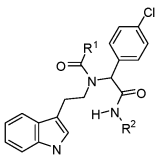
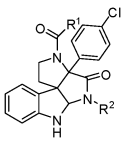
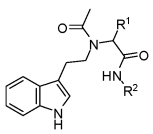
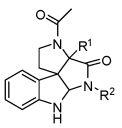
Table 2 Scope of the oxidative process

Entry	Ugi adduct (yields)	Cyclized product (yields)
		
1	**1b** R = Et 89%	N.R.
2	**1c** R = 4-ClC_6H_4 89%	**2c** R = 4-ClC_6H_4 64%
3	**1d** R = 4-$MeOC_6H_4$ 83%	**2d** R = 4-$MeOC_6H_4$ 53%
4	**1e** R = 4-HOC_6H_4 93%	**2e** R = 4-HOC_6H_4 62%
5	**1f** R = 4-$NO_2C_6H_4$ 90%	**2f** R = 4-$NO_2C_6H_4$ 76%
		
6	**1g** X = H 93%	**2g** X = H 66%
7	**1h** X = Cl 88%	**2h** X = Cl 75%
8	**1i** X = OMe 83%	**2i** X = OMe 59%
		
9	**1j** R^1 = Me, R^2 = *t*-Bu 94%	**2j** R^1 = Me, R^2 = *t*-Bu 66%
10	**1m** R^1 = Ph, R^2 = Cy 90%	**2m** R^1 = Ph, R^2 = Cy 60%
		
11	**1k** R^1 = 2-pyridyl, R^2 = Cy 90%	**2k** R^1 = 2-pyridyl, R^2 = Cy 46%
12	**1l** R^1 = 2-pyridyl, R^2 = Cy 93%	**2l** R^1 = 2-pyridyl, R^2 = Cy 37%

should be much more acidic. However, aromatic substituents bearing either electron-donating or electron-withdrawing groups were introduced successfully at this position. The reaction proceeded efficiently with various amide substituents, even hindered ones.

It is worth noting that, probably due to an easier enolization, compound **1f** (with a nitro group) could be oxidized under non-basic and even acidic conditions. Indeed, when treated with one equivalent of copper diacetate in acetic acid at reflux for 20 h, the corresponding **2f** was obtained in 54% yield. The reaction was even more efficient in acetonitrile, with **2f** being formed in 80% isolated yield after 8 h at room temperature. The structures of compounds **2** were confirmed by an X-ray analysis of **2f** (Fig. 1).

Most synthetic strategies for spiroindolines rely on a spirocyclization process onto the C-3 of the indole nucleus *via* a dearomatization process.[6,11,12] Since the pioneering work of a C-3 iminium-mediated spirocyclization of tryptamine derivatives to obtain spiroindolenines, as reported by Van Tamelen *et al.*,[11] the process has been expanded with

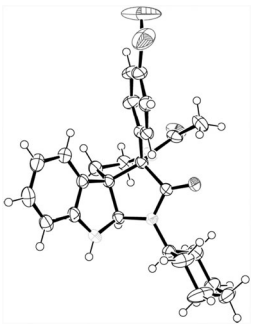
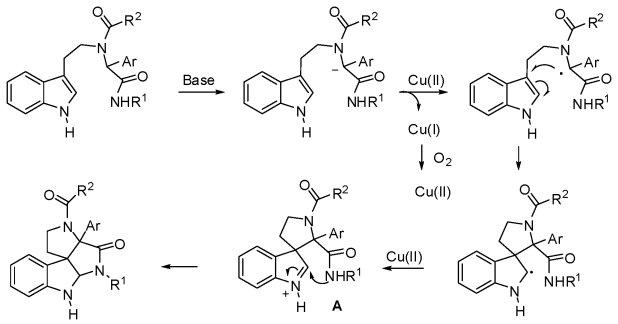


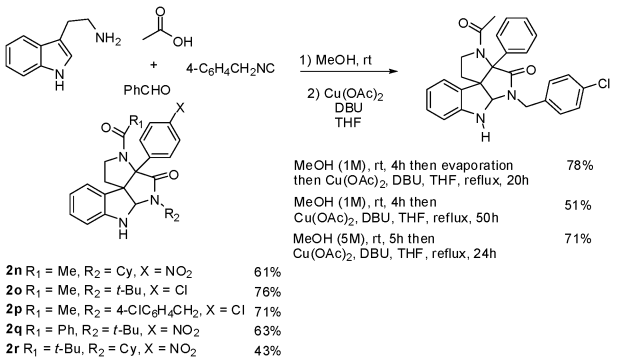
Fig. 1 X-Ray analysis of **2f**.



Scheme 1 Proposed radical mechanism.

modern technologies. Several elegant C-3 selective Pd- and Ir-catalyzed allylations of indoles using different sources of allylic cations have been reported to construct a range of indolenine and indoline derivatives bearing quaternary stereocenters.[12] Less studied have been the free radical-mediated C-3 spirocyclization processes of indole derivatives leading in our case to a radical analogue of a Pictet–Spengler cyclization.[6,9b] The reaction mechanism probably involves the oxidative generation of a peptidyl radical triggered by copper(II) salts. A 5-*exo*-dig cyclization, followed by a further oxidation of the α-aminoalkyl radical forms an iminium trapped by the vicinal amide moiety (Scheme 1). This mechanism is supported by known radical additions onto the indole core[9] as well as recent oxidative couplings of radicals generated from enolates.[13] The reaction shares some relationship with the anionic couplings reported by the Baran group.[14] In our case, the choice of an aryl activating group in the peptidyl position allowed a coupling under mild basic conditions.[15] We were able to eliminate the possibility of alternative mechanistic paths starting from an oxidation of the indole core based on the reactivity of **1f** under neutral conditions compared to the unproductive coupling of **1a** in the absence of a base.[16]

Considering the high level of diversity offered by this oxidation–cyclization process, we were eager to adapt the procedure and transform it into a one-pot process. Although we were unable to identify a solvent applicable for both steps, we were delighted to find that the oxidation could be performed directly after the Ugi reaction without any intermediate purification. The best yields were obtained by simply evaporating the methanol. More conveniently, the first step may be performed in a more concentrated medium, followed by direct addition of THF, base and copper (Scheme 2).



Scheme 2 One-pot conditions for the preparation of spiroindolines.

In conclusion, we have disclosed a new copper-catalyzed spirocyclization. The reaction probably involves radicals generated from enolates by a copper(II)-triggered oxidation. This simple procedure produces remarkably complex final structures. In these one-pot reactions, the four-component nature of the first Ugi step contributes to the formation of complex alkaloid-like structures with high diversity. The programmed combination of this multi-component reaction with sequential secondary transformations has already been recognized as a powerful approach to reach high molecular complexity. Indeed, many cycloadditions, cyclocondensations or organometallic couplings have been reported as Ugi post-condensations. In contrast, radical cyclizations still remain underutilized.[7,17] This new synthesis of complex indolines in one step underscores the potential of such synthetic approaches.

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15 The fact that the reaction only gives one diastereomer is rather surprising for the cyclization of a radical species. It may be explained either by a degradation of the isomer unable to cyclize with the pendant amide or by a ring-opening of the spiro iminium **A** leading to an epimerization of the peptidyl position.

16 **1f** is probably oxidized *via* its enol tautomer.

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