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A thiol-mediated three-step ring expansion cascade for the conversion of indoles into functionalised quinolines

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ABSTRACT: An operationally simple, high yielding three-step cascade process is described for the direct conversion of indole-tethered ynones into functionalised quinolines. A single ‘multi-tasking’ thiol reagent is used to promote a three-step dearomatising spirocyclisation, nucleophilic substitution and one-atom ring expansion reaction cascade under remarkably mild conditions. In addition, a novel route to thio-oxindoles is described, which was discovered by serendipity.

Cascade reactions (chemical processes by which two or more consecutive reactions take place in a single pot-process, also known as ‘tandem’ or ‘domino’ reactions) have wide utility in synthetic chemistry. Incorporating cascade reaction sequences into synthetic routes can significantly improve the speed and ease with which complex target molecules can be prepared, and often means that the direct handling of reactive, unstable and/or toxic species can be avoided by forming these intermediates in situ.

This manuscript concerns a three-step cascade reaction sequence, starting from indole-tethered ynones 1 (Scheme 1). In recent years, ynones of this type have emerged as valuable precursors for the preparation of a diverse array of molecular scaffolds. For example, our groups and others have shown that the activation of the alkyne moiety of 1 promotes efficient dearomatising spirocyclisation to form medicinally important spirocyclic indolenines 2, which is most commonly done using π-acidic catalysts (especially Ag(I) species), although Brønsted acids, palladium(II) complexes and electrophilic halogenation reagents can also be used (1 → 2, Scheme 1a, Step 1). Our groups have also shown that dearmatisation works well on 2-halogenated indoles (i.e. 1 where X = Cl, Br or I) and that the resulting indoleninyl halide products (i.e. 2 where X = Cl, Br or I) can be transformed further via reaction with nucleophiles, or via Pd-catalysed cross-coupling, to substitute the halide for various other groups (2 → 3, Scheme 1a, Step 2). Finally, our groups and others have demonstrated that spirocyclidene indolenines of the form 3 will rearrange via a one-atom ring expansion to form annulated quinolines, with both acidic and basic reagents able to promote this transformation (3 → 4, Scheme 1a, Step 3).

Efficient protocols for each of the individual steps represented in Scheme 1a are therefore established, but three-steps are still required to generate functionalised quinolines 4 from ynones 1. Quinolines are found in many marketed drugs, as well as in various other applications. Based on a growing understanding of each of the three individual processes discussed above, we recognised that certain reagents may be able to promote all three steps and enable the transformation of 1 into 4 via a single-cascade process (Scheme 1b): such a reagent would need to act as an acid to promote step 1, a nucleophile in step 2, and a Bronsted acid to promote step 3. The successful realisation of this strategy is reported herein, with thiolos emerging as the optimum ‘multi-tasking’ reagent class capable of promoting the envisaged cascade, under remarkably mild and operationally simple conditions.

We started by exploring reactivity of model 2-bromo ynone 1a with various reagents (NuH) that we thought might have the required acidity and nucleophilicity to promote its conversion into a quinoline of the form 4. Phenol was tested first, and added to a solution of 1a in DCE, but no reaction was observed after stirring at RT or 60 °C (entries 1 and 2, Table 1). Next, TFA was included as an additive and the reaction, which led to the consumption of the starting material, but the only tractable products observed were oxindole 7a (presumably formed via acid-mediated dearmatisation spirocyclisation and hydrolysis of the resulting spirocycle 5a), and bromoquinoline 8, which likely formed via a Bronsted acid-mediated rearrangement of 5a (cf. step 3). A more acidic NuH reagent, 4-nitrophenol, was tested but no reaction was observed at RT (entry 4), while at 60 °C the same side products 7a and 8 were formed (entry 5). We then decided to move on to species of similarly acidity to phenol, but also more nucleophilic, and pleasingly, thiolos were found to possess this attractive combination of properties; using n-propyl thiol, no conversion was observed at RT (entry 6), but excellent conversion into the desired quinoline 4a was observed upon heating to 60 °C (entry 7). Furthermore, the more acidic thiophenol was able to promote the conversion of 1a into quinoline 4b smoothly at RT (entry 8).
Table 1. Initial optimisation\(^{[a]}\)

| entry | Nucleophile (\(\text{NuH}\))       | Temp  | Outcome\(^{[b]}\) |
|-------|----------------------------------|-------|------------------|
| 1     | Phenol (\(\text{Nu} = \text{PhO}\)) | RT    | No reaction      |
| 2     | Phenol (\(\text{Nu} = \text{PhO}\)) | 60 °C | No reaction      |
| 3     | Phenol (\(\text{Nu} = \text{PhO}\)) with 1 equiv. TFA | RT    | 7a (62%)         |
| 4     | 4-Nitrophenol (\(\text{Nu} = \text{4-NO}_{2}\text{C}_{6}\text{H}_{5}\)) | RT    | No reaction      |
| 5     | 4-Nitrophenol (\(\text{Nu} = \text{4-NO}_{2}\text{C}_{6}\text{H}_{5}\)) | 60 °C | 7a (35%)         |
| 6     | \(n\)-Propyl thiol (\(\text{Nu} = \text{n-PrS}\)) | RT    | No reaction      |
| 7     | \(n\)-Propyl thiol (\(\text{Nu} = \text{n-PrS}\)) | 60 °C | 4a (95%)         |
| 8     | Thiophenol (\(\text{Nu} = \text{PhS}\)) | RT    | 4b (93%)         |

\(^{[a]}\) 1a_{Br} (1 equiv) and \(\text{NuH}\) (1.6 equiv) were stirred in DCE (0.1 M, degassed) for 20 h at the specified temperature. \(^{[b]}\) Yields are isolated material after column chromatography.

With conditions for the cascade established, attention turned to examining the reaction scope. A range of aromatic thiols were tested (Scheme 2A), and all reacted well with ynone 1a_{Br}; quinolines 4b-k were all prepared in this manner, generally in high yield, under the standard RT conditions using a range of electronically diverse substituted thiophenols. Other aliphatic thiols were also explored, with quinolines 4a, and 41-n prepared, although in this series heating to 60 °C was required. The yield for quinoline 4n was comparatively low (53%), with thio-oxindole 9a also formed in 27% yield; this unexpected side reaction is discussed later in the manuscript (see Scheme 3).\(^{17}\)

Next, the 2-halide substituent was varied (Scheme 2B). Thus, 2-chloro (1a) and 2-iodo (1a) analogues of ynone 1a_{Br} were prepared,\(^{4}\) and both reacted smoothly with 4-methylbenzenethiol to form quinoline 4d in high yield, albeit at a higher reaction temperature (60 °C). Finally, we explored variation of the indole-tethered ynone component 1. Four different additional 2-bromo-indole-tethered ynones were successfully tested, with variations to the ynone and the indole motifs explored. For each ynone, a representative aliphatic (\(n\)-propylthiol) and aromatic thiol (4-methylbenzenethiol) were tested, with the expected quinoline products 4o-v to be isolated successfully in all cases.\(^{18}\) The only substrate tested that did not deliver the expected quinoline was 4-NMe\(_2\)-substituted ynone 1f; in this case, spirocyclic indoleninyl bromide 5b was isolated in 89% yield.\(^{19}\) Despite not delivering the expected quinoline, the isolation of spirocycle 5b does provide indirect mechanistic evidence for the intermediacy of indoleninyl halides in the reaction cascade (see later for discussion). Finally, by replacing the thiol with benzene selenium, the analogous selenide product 4bs was obtained in 62% yield.

The unexpected isolation of thio-oxindole 9a during the synthesis of 4n prompted additional studies, in part to better understand this side reaction, but also to try and harness it productively, as a new way to make thio-oxindoles.\(^{20}\) Our theory for how thio-oxindole 9a formed is summarised in Scheme 3a. The reaction is likely to have started as expected, and thus proceeded through the normal dearomatising spirocyclisation and nucleophilic substitution steps (i.e. steps 1 and 2). This would generate spirocycle 10, and at this point, it appears that the route diverges, with some of the material going on to form quinoline 4n in the usual way, and the rest undergoing debenzylation, either via an S1-type pathway as drawn, or the analogous S2-type cleavage (not shown). To test this idea and improve the yield of thio-oxindole 9a, the reaction was repeated using the silylated thiol \(\text{PhS}:\text{SiSH}\) 11; the idea was that the weak Si–S would cleave more easily than the S–Bn bond in 10, and facilitate thio-oxindole formation via a desilylative mechanism. This idea worked well; the reaction of ynone 1a_{Br} with \(\text{PhS}:\text{SiSH}\) 11 using the standard 60 °C procedure led to the formation of thio-oxindole 9a in 82% isolated yield (Scheme 3b). The same procedure was applied to other 2-halo-indole-tethered ynones, with thio-oxindoles 9b–9d (47–85%) prepared in the same way.

A proposed mechanism for the three-step cascade is outlined in Scheme 4a. The cascade likely initiates with dearomatising spirocyclisation, promoted by the relatively acidic thiol (\(A \rightarrow B\), step 1, Scheme 4a); protic acids have been shown to promote spirocyclisation of related ynones,\(^{23,24}\) and the isolation of spirocyclic indoleninyl bromide 5b discussed earlier lends further support to this notion. The resulting iminium-thiolate ion pair 2 may then undergo facile nucleophilic substitution to afford substituted spirocycle 12 (step 2).\(^5\) The rearrangement of 12 into 17 is then thought to proceed via a previously studied acid-catalysed one-atm ring-expansion.\(^{25}\)

Several control experiments were conducted to investigate this mechanism and the ordering of the steps. First, to probe whether the nucleophilic substitution step may proceed before spirocyclisation, 2-bromo-indole substrates lacking an ynone substituent (18 and 21) were each reacted under the standard conditions with 4-methylbenzenethiol (Scheme 4b, eq 1). In the case of indole 18, some bromide substitution was indeed observed, with sulfide 19 formed in 31% yield. This confirms that nucleophilic substitution directly on the indole is possible, although the yield was low, and the major product was in fact the reduced product 20. Treating the analogous 3-methyl indole 21 in the same way resulted in the formation of 22 only. In view of these results, and given that no reduction products were observed in any of the synthetic reactions, it seems unlikely that nucleophilic substitution precedes dearomatising spirocyclisation.
We then questioned whether the iminium-thiolate ion pair B might first undergo ring expansion to form a quinoline and that nucleophilic substitution follows this step. To probe this idea, both indoleninyl bromide 5a and 2-bromoquinoline 8 were reacted with 4-methylbenzenethiol under the standard reaction conditions. Interestingly, both reactions afforded the expected quinoline product 4a in high yields (Scheme 4b, eqs 2 & 3), suggesting that the order of steps 2 and 3 could be interchanged.

To investigate this idea further, a discrete sample of the substituted spirocyclic sulfide 6a was reacted with 4-methylbenzenethiol under the standard reaction conditions (eq 4). No conversion into quinoline 4a was observed and only 6a was recovered after stirring for 24 h at both RT and 60 °C. However, the quinoline product 4a could be formed in high yield at RT upon the addition of 1.1 equivalents of 48% aq HBr to spirocyclic sulfide 6a. This result suggests that a strong Brønsted acid is required to promote the ring expansion, and such an acid would only be present in the reaction following the nucleophilic substitution step (which generates HX), thus supporting the originally proposed order of steps. Furthermore, the success of the series of thioxindole forming reactions described in Scheme 3 also supports the same pathway, because in these reactions the successful formation of spirocyclic products 9a–d means that nucleophilic substitution must have out-competed ring expansion in these cases.
Scheme 3. The conversion of ynone 1 into thio-oxindoles 9 via a desilylative cascade process.\(^\text{[a]}\)

\[ \text{STEPS 1-2} \]

1\(_{\text{Ar}}\) + HSC\(_{\text{S}}\) \(\rightarrow\) Ph

DCE, 60 °C

\[ \text{PhCH}_{2}^{+} \rightarrow \text{Ph} \]

Considering all these observations, we can be confident that the first step of the cascade is a thiol-promoted de-aromatising spirocyclisation (step 1). The next step is most likely to be nucleophilic substitution (step 2) of the resultant iminium-thiolate ion pair, which generates a strong Brønsted acid (HBr) in situ. This acid then promotes a one-atom ring expansion (step 3) to form a stable aromatic quinoline product 4. Some interchange in the ordering of steps 2 and 3 cannot be ruled out once a reasonable concentration of HBr has built up in the reaction, however.

In summary, a three-step cascade process has been developed that allows for the direct conversion of 2-halo-indole-tethered ynone into substituted quinolines. The key to the process is the use of thiols as 'multi-tasking' reagents able to promote de-aromatising spirocyclisation and nucleophilic substitution directly, as well promoting a one atom ring expansion indirectly, via the formation of a strong Brønsted acid (HBr) in situ. The reactions are very simple to perform\(^\text{21}\) and are typically high yielding, enabling the facile synthesis of a diverse array of functionalised quinolines. They are also easily scalable; for example, quinoline 4d was formed in 97% yield on 1 mmol scale (see ESI). In addition, a related route to thio-oxindoles was also developed following a serendipitous discovery of an unexpected side reaction.

ASSOCIATED CONTENT
Supporting Information. Experimental procedures, characterisation and copies of \(^{1}H\) and \(^{13}C\) NMR spectra for all compounds featured in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org

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Scheme 4. Proposed mechanism and control reactions

a) Proposed mechanism

b) Control reactions

\[ \text{Conditions} \]

DCE, 24 h, RT

\[ \text{Conditions} \]

DCE, 24 h, RT

\[ \text{Conditions} \]

DCE, 60 °C

\[ \text{Conditions} \]

DCE, 60 °C

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15) DCE (1,2-dichloroethane) was chosen as solvent due to its relatively wide temperature range and efficacy in a recent study involving indole-tethered yrones (see reference 4a). The cascade reactions also works well when DCM is used in place of DCE (84% isolated yield for the conversion of 1aBr into 4b), but the use of the non-chlorinated solvents THF and acetone for the same reaction was far less effective (no reaction and 20% yield of 6a respectively).

16) For an interesting recent study on thiol mediated cascade reactions of alkyne-based precursors, that operates via a radical mechanism, see: Dutta, S.; Mallick, R. J.; Prasad, R.; Gandon, V.; Sahoo, A. K. Alkynyl Versus Ynamic Reactivity: Regioselective Radical Cyclization of Yne-Nynamides. Angew. Chem. Int. Ed. 2019, 58, 2289–2294.

17) For examples and perspective on synthetic processes discovered by serendipitous/unforeseen processes, see reference 4a and: (a) Zard, S. Z.; New syntheses of alkenes: a tale of serendipity and design. Chem. Commun. 2002, 1555; (b) Grimes, R. N. Synthesis and serendipity in boron chemistry: A 50 year perspective. J. Organomet. Chem. 2013, 747, 4; (c) Unsworth, W. P. Taylor, R. J. K. Uopenamide: trials and tribulations Org. Biomol. Chem. 2013, 11, 7250–7261 (d) Kazim, M.; Siegler, M. A.; Lectka, T. A Case of Serendipity: Synthesis, Characterization, and Unique Chemistry of a Stable, Ring-Unsubstituted Aliphatic p-Quinone Methide. Org. Lett. 2019, 21, 2326; (e) Strieder-Kalthof, F.; Henkel, C.; Teders, M.; Kahnt, A.; Knolle, W.; Gómez-Suárez, A.; Dirian, K.; Alex, W.; Bergander, K.; Danilici, C. G.; Abel, B.; Guldó, D. M.; Glorius, F. Discovery of Unforeseen Energy-Transfer-Based Transformations Using a Combined Screening Approach. Chem. 2019, 5, 2183.

18) CCDC 2054407 contains the crystallographic data for compound 4v, see: www.ccdc.cam.ac.uk/data request/cif

19) The reason for this difference is not fully clear. Solubility differences and/or changes to the electronic properties of the ynone may both have had an influence, while the relatively basic aniline group may also have altered the pH balance and affected proton transfer in the reaction. Notably, in previous studies we have found that other 4-NMe2-substituted yrones have also reacted differently to other seemingly similar substrates in the series (see reference 6a).

20) For background and biological properties of thio-oxindoles and related oxindoles, see: Hurst, T. E.; Gorman, R. M. Drouhin, P.; Perry, A.; Taylor, R. J. K. A Direct C–H/Ar–H Coupling Approach to Oxindoles, Thio–oxindoles, 3,4-Dihydro–1H-quinolin–2-ones, and 1,2,3,4-Tetrahydro–quinolines. Chem. Eur. J. 2014, 20, 14603–14703 and reference therein.

21) Although degassed solvent was typically used in this study to help ensure consistent results, this level of precaution is generally not needed; for example, the conversion of 1aBr into 4d worked in 98% yield when done without degassing. The insensitivity of the reaction to oxygen also suggests that alternative radical pathways (c.f. reference 4a) are unlikely to operate. In addition, it was found that ynone 1aBr does not react when treated with PhSSPh in place of PhSH under the standard RT conditions, which further reduces the likelihood that the cascade reaction involves thyl radical intermediates. The analogous reaction with PhSSPh and 1 equivalent of HBr led only to the formation of products in which sulfur had not been incorporated: 7a (18%) and 8 (72%).
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