Visible-light-induced intramolecular charge transfer in the radical spirocyclisation of indole-tethered ynones†

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Indole-tethered ynones form an intramolecular electron donor–acceptor complex that can undergo visible-light-induced charge transfer to promote thyl radical generation from thiols. This initiates a novel radical chain sequence, based on dearomatising spirocyclisation with concomitant C–S bond formation. Sulfur-containing spirocycles are formed in high yields using this simple and mild synthetic protocol, in which neither transition metal catalysts nor photocatalysts are required. The proposed mechanism is supported by various mechanistic studies, and the unusual radical initiation mode represents only the second report of the use of an intramolecular electron donor–acceptor complex in synthesis.

Introduction

The use of visible-light-mediated photochemistry in synthesis has grown enormously in recent years,1,2 triggered by dramatic progress in the fields of photoredox catalysis,3 energy transfer4 and atom transfer processes.5 This has led to a renaissance in the use of single electron transfer (SET) processes in chemical synthesis, including renewed interest in the study of charge transfer in electron donor–acceptor (EDA) complexes.

The phenomenon of charge transfer was first postulated in the 1950s,6,7 but received relatively little attention in synthetic chemistry8 until a surge in interest in the last decade,9 with an illustrative example recently reported by Glorius and co-workers summarised in Scheme 1a.10 In this study, it was shown that the coupling of indoles 1 and pyridinium salt acceptors 2 can be performed in the absence of a transition metal catalyst or photocatalyst. Key to this process is the formation of an intramolecular EDA complex A between an indole (the donor) and a pyridinium salt (the acceptor); the EDA complex can then absorb visible light to promote charge transfer to form radical 4, that can then fragment to give electrophilic radical 5 and couple with indole 1 to afford C-2 functionalised indole 3 via a radical chain process.

This report and others,9,10 highlight the value of intermolecular EDA-mediated charge transfer for the construction of challenging chemical bonds. However, until a 2018 report by

Scheme 1. EDA complexes in synthetic chemistry (a, b = previous work, c = this work). DCE = 1,2-dichloroethane. LED = light emitting diode.
Melchiorre and co-workers,\textsuperscript{11,12} there were no reports of the use of photon-absorbing \textit{intramolecular} EDA complexes being used in synthesis. In this seminal study, an enantioselective radical conjugate addition reaction is described that relies on visible-light-excitation of a chiral iminium-ion based intramolecular EDA complex \textbf{B}, itself formed \textit{in situ} from a ketone \textbf{6} and organocatalyst \textbf{8} (Scheme 1b).\textsuperscript{11}

Herein, a new synthetic method based on \textit{intramolecular} EDA complexation and charge transfer is reported for only the second time. Thus, a novel radical dearomatising spirocyclisation\textsuperscript{13} of indole-tethered ynone 10 (ref. 14) and thiols 11 is described for the formation of spirocyclic indolines 12 with concomitant C-S bond formation (Scheme 1c).\textsuperscript{13} The reactions are catalyst-free and proceed \textit{via} a thyl radical-based chain process, that is thought to be self-initiated by the ynone starting material 10, through visible-light-induced charge transfer of an intramolecular EDA complex \textbf{C}. A wide range of sulfur-containing spirocycles 12 have been prepared using this mild, high yielding synthetic procedure. This unusual photocatalyst-free method to initiate radical chemistry was discovered by serendipity, and could easily have gone unnoticed, if not for the recent surge in interest in the study of charge transfer in electron donor–acceptor (EDA) complexes.

results and discussion

The original aim of this project was to develop a radical spirocyclisation protocol based on more well-established methods for radical generation. We postulated that indole-tethered ynone 13 would react with electrophilic radicals \textit{via} regioselective addition to the alkyne group (13 \textit{→} 14), before cyclising on to the indole at its 3-position to form a spirocyclic radical intermediate (14 \textit{→} 15). Radical 15 could then go on to form either spirocyclic indoline 16 \textit{via} hydrogen atom transfer (HAT), or spirocyclic indoline 18 \textit{via} single electron oxidation followed by proton loss (Scheme 2). Oxidation of 16 to 18 in the presence of molecular oxygen, or other oxidants, was also predicted to be viable. Confidence in this general idea was raised by reports of radical-based dearomative processes involving phenol- and anisole-tethered alkenes.\textsuperscript{16,17} These studies confirm that electrophilic radicals can react with ynones with the desired regioselectivity, and that the so-formed radical species can go on to react with tethered aromatics; however, to the best of our knowledge, such a strategy had not been applied to indole-tethered alkenes prior to this report.

This study began by examining the reaction of ynone 13a with a thyl radical generated from thiophenol \textit{in situ}. Thyl radicals are versatile reactive intermediates in synthetic radical chemistry\textsuperscript{18} and we reasoned that the derived products could be relevant in drug discovery, in view of the prevalence of vinyl sulfides in bioactive compounds.\textsuperscript{19} A photoredox catalysis approach originally was chosen to generate the thyl radical,\textsuperscript{20} which led to the development of the conditions summarised in Scheme 3 (see ESI\textsuperscript{†} for full optimisation). Thus, the combination of thiophenol, catalytic Ru(bpy)\textsubscript{3}(PF\textsubscript{6})\textsubscript{2} and irradiation with a blue LED lamp (\(\lambda_{\text{max}} = 455\) nm, 60 W) at rt under air, enabled the conversion of indole-tethered ynone 13a into spirocyclic indoline\textsuperscript{21} 18a in reasonable yield \textit{via} an overall oxidative dearomative process (Scheme 3, a). Product 18a was synthesised along with indoline 16a as minor side-product, with 16a believed to be an intermediate on the route to indolene 18a.\textsuperscript{22} Control experiments revealed that oxygen is required for the efficient formation of 18a (indoline 16a is the major product in the absence of oxygen, Scheme 3, d) and more intriguingly, a mixture of both products 18a and 16a is formed \textit{even in the absence of any photocatalyst} (Scheme 3, e). In the absence of light, no reaction occurs (Scheme 3, f). This indolene-forming reaction was also found to work on other ynone starting materials (5 examples, see ESI\textsuperscript{†} page S8 for details).

The unexpected discovery that spirocyclisation can be achieved without Ru(bpy)\textsubscript{3}(PF\textsubscript{6})\textsubscript{2} was intriguing, both from a mechanistic standpoint, and in view of the clear practical and environmental benefits of avoiding metal-based photocatalysts. We therefore decided to explore this process in more detail and started by establishing whether the photocatalyst-free reaction conditions could be applied to other substrates. Additional optimisation was performed at this point (see ESI\textsuperscript{†}), and based on this, the decision was made to prioritise the synthesis of indoline products 16/19 \textit{via} overall redox neutral reactions, \textit{c.f.} Scheme 3, d) rather than indolenes 18 (overall oxidative processes, \textit{c.f.} Scheme 3, a).\textsuperscript{23} Thus, the reactions were performed under argon rather than air; another change to the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_3}
\caption{Control reactions; all yields are based on comparison to an internal standard in the \textsuperscript{1}H NMR spectrum of the unpurified reaction mixture except for ‘a’ which is an isolated yield. CFL = compact fluorescent lamp.}
\end{figure}
conditions was to switch the solvent from acetonitrile to 1,2-dichloroethane (see ESI† for further optimisation details).

The optimised conditions were then tested across a range of indole-tethered ynone and thiols, and the results summarised in Scheme 4 confirm that the reaction is broad in scope. Changes to the substituent on the indole nitrogen (NH and NMe), the indole 2-position and the ynone terminus (R3) were all tolerated (16a–n, 15–99%), with bulky TIPS-substituted ynone 13o (to form 16o) the only unsuccessful example. In cases where the indole C-2 position is substituted (16a–f) the products were isolated as the single diastereoisomer shown, with the assignment of relative stereochemistry based on X-ray crystallographic data for 16a.24,25

The reactions also work well with a range of thiols (20 examples, 19a–19t, 36–99%). Various electronically diverse, substituted arylthiols were well-tolerated (19a–19j), with the more electron-rich examples typically the highest yielding. We were also pleased to observe that aliphatic thiols are compatible with the standard procedure (19k–19p); the S–H dissociation energy (BDE) for alkyl thiols (~87 kcal mol⁻¹) is usually higher than related aryl thiols (72–82 kcal mol⁻¹), which can adversely affect their reactivity in radical reactions.18 More complex thiols have also been shown to work well using the standard procedure, including 1,3-propanedithiol (to make dimeric product 19r), a protected cysteine derivative and a peptide-like thiol (to make 19q and 19s) and an α-tocopherol-derivative thiol (to make 19t).

Having established the synthetic method, attention then turned to understanding how the reactions operate in the absence of photocatalyst. We reasoned that visible-light activation of one of the starting materials must play a key role. Based on precedent, several possibilities could be envisaged:26,27 (1) light-induced homolytic cleavage of the thiol S–H bond to generate a thiyl radical would account for the observed reactivity, as this could start a radical chain reaction, as outlined earlier in Scheme 2; (2) similar reactivity could also originate from homolytic S–S bond cleavage of trace disulfides present in the thiol reagent; (3) photoexcitation of the alkyne to its triplet state could form an open-shell species theoretically capable of initiating radical chemistry.

Although we considered all of these scenarios to be unlikely under the influence of blue light (based on the energy typically needed to homolyse S–H/S–S bonds or to electronically excite alkynes),18,27 control experiments were nonetheless designed to

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**Scheme 4** Light induced charge-transfer radical spirocyclisation. Isolated yields following column chromatography are given.
examine these possibilities. The experiments were based on the
hydrothiolation of simple alkynes; thus, each of alkynes 20 and
22 were reacted with n-propane thiol under blue LED irradiation
at RT, but no conversion into vinyl sulfides 21 and 23 was
observed, with the alkynes fully recovered in each case (Schemes
5a and 5b). The lack of hydrothiolation in these experiments
supports the idea that the initiation mechanisms suggested
above are invalid; thyl radicals seem not to be formed directly
from the thiol reagent (or trace amounts of disulfides) in the
presence of either of these alkynes, and the lack of reactivity
observed with ynone starting material 20, appears to rule out
simple triplet excitation of the ynone functionality under blue
light radiation. Instead, these results suggest that the indole-
tethered ynone moiety 13 itself is critical to the observed reac-
tivity. Indeed, compelling evidence that supports the involve-
ment of the ynone in initiating thyl radical chemistry was
obtained when alkynes 20 and 22 were again reacted with n-
propane thiol, but this time with the addition of sub-
stoichiometric (20 mol%) ynone 13k; under these conditions,
hydrothiolation products 21 and 23 were obtained in 54% and
80% yields, respectively.

Normally, neither ynones nor 3-substituted indoles would be
expected to absorb visible light wavelength photons. However,
the ynones 13 used in this study tend to be yellow in colour, and
indeed, ynone 13g was found to absorb relatively strongly at
around 455 nm (the $\lambda_{\text{max}}$ of the light source) when analysed
using UV-Vis spectroscopy (orange line, Scheme 5c; for the
emission spectra of 13g see the ESI†). In contrast, model ynone
20 (blue line), 3-substituted indole 24 (cyan line), and thio-
phenol 11a (black line) displayed little/no absorption in the
same region. Equimolar mixtures of these compounds (20 + 11a
in grey, 20 + 24 in pink and 24 + 11a in green) did absorb in the
visible region when measured at 0.02 M, although interestingly,
when mixed at much higher concentration (>0.5 M) a significant
bathochromic shift was observed for a mixture of ynone 20 and
indole 24, indicating that the intermolecular interaction of
these components can influence their absorption properties,
albeit at concentrations well above those used in the synthetic
reactions (see ESI, Scheme S4†). The addition of thiol 11a does
not appear to influence the absorbance, with near-identical UV-
Vis spectra obtained for both ynone 13k and a mixture of 20 and
24, with and without the inclusion of 11a (see ESI Scheme S4†).

The ability of the indole ynone starting materials 13 to
absorb visible light around 455 nm appears to correlate well
with the success of the radical cascade processes, as illustrated
by the data presented in Scheme 5d. For example, alkynes 13p
and 13q, showed low absorption at 455 nm (purple and blue
lines respectively) and both the conversion and yields for these
reactions were much lower than those for the standard
substrates (c.f. Scheme 4).28 In contrast, ynones 13g, 13k and

Scheme 5  (a) Hydrothiolation of ynone 20; (b) Hydrothiolation of alkyne 22; (c) UV-Vis spectroscopy studies of indole-tethered ynone 13g
compared with model reaction components; (d) UV-Vis spectroscopy of indole-tethered ynones (13g, 13k, 13l, 13p) and propargylic alcohol 13q.
All UV-Vis experiments were performed in anhydrous 1,2-dichloroethane (0.02 M).
13i, which all reacted efficiently to form 16g, 16k and 16l with full conversion and in good yields, show a clear red-shift into the visible region (orange, red and green lines respectively).29

We postulate that through-space interactions explain the enhanced visible light absorption of the reactive ynone systems, via formation of an intramolecular EDA complex of the form C (Scheme 6a) that enables the ynone to absorb relatively long wavelength visible light and initiate thyl radical chemistry. A through bond process (i.e. involving conjugation via enolate formation)26 was also considered as a possible explanation for the red shift of typical ynone substrates, but was ruled out on the basis of the UV-Vis data and successful reaction of non-enolisable ynone 13i. The formation of an intramolecular EDA complex is also supported by time-dependent density functional theory (TDDFT) calculations performed on ynone 13k, which predicted a peak at 441 nm with an oscillator strength of 0.050 (Scheme 6b). This peak is composed entirely of a charge transfer excitation between the π orbitals of the indole HOMO and ynone LUMO (Scheme 6b).

Thus, a mechanism is proposed in which the formation of an EDA complex C is followed by visible light absorption to form a photoexcited state, loosely represented as charge transfer complex 25. This species may simply relax to reform EDA complex C via back electron transfer, or alternatively, the open shell excited state 25 could abstract a hydrogen atom from the thiol 11, thus generating the thyl radical needed to start a radical cascade (Scheme 6a).31 At this point, a more typical radical chain process can operate (Scheme 6c), which likely proceeds by the addition of thyl radical to the ynone (10 → 26), spirocyclisation (26 → 27) and hydrogen atom abstraction from thiol 11 (27 → 12), thus enabling chain propagation. Quantum yield measurements (ϕ = 19.8)32 support operation through a chain process.33,34

Conclusions

In summary, a new dearomative method for the synthesis of sulfur-containing spirocyclic indolines is described, based on the reaction of indole-tethered ynones with thyl radicals generated in situ from thiols. The reactions are promoted by visible light, operate at RT under mild reaction conditions and need neither a transition metal catalyst nor added photocatalyst to proceed efficiently across a wide range of substrates. The reaction is thought to be self-initiated35 with visible-light-mediated photoexcitation of an intramolecular EDA complex formed between the indole and ynone moieties in the starting material leading to the formation an open shell excited charge-transfer complex, capable of abstracting a hydrogen atom from the thiol and initiating radical chain propagation.

To the best of our knowledge, this is only the second report that details the use of intramolecular EDA complexes in synthesis. This rare radical activation mode was uncovered entirely by serendipity,36 and this is a feature of the discovery that we are keen to highlight, as we believe that intramolecular EDA complexes likely play key roles in other synthetic methods, but can go (or have gone) unnoticed.3rd As awareness of the value of charge transfer processes in synthetic chemistry grows, we believe that many important new methods of this type will be discovered, both through design and by serendipity.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

2 For selected reviews of visible light photocatalysis, see: (a) T. P. Yoon, M. A. Ischay and J. Du, Nat. Chem., 2010, 2,


For examples of radical-based deaeromatization processes involving phenol- and anisole-tethered alkynes, see: (a) W. Wei, H. Cui, D. Yang, H. Yue, C. He, Y. Zhang and H. Wang, Green Chem., 2017, 19, 5608; (b) Y. Zhang,

17 For a relevant process based on a visible light mediated thyl radical annulation of alkyn-terminated thiolen-olines, see: K. Kim, H. Choi, D. Kang and S. Hong, *Org. Lett.*, 2019, 21, 3417. EDA complex activation in the ground state was ruled out in this study.


22 Re-subjecting an isolated sample of 16a to the reaction conditions led to full conversion into indoline 18a over time, with atmospheric oxygen the likely oxidant (see ESI† for further details).

23 We reasoned that running the reactions under argon rather than air would lead to a more reproducible procedure, and we also know that spirolindolines can be easily prepared by oxidation of the corresponding spiroindolines if required (see ESI†).

24 CCDC 1945619 (16a), 1945618 (16j), 1945660 (16g), 1645620 (13g), and 1645621 (13k) contain the crystallographic data, see ESI†.

25 When an analogous ynone substrate (13r) bearing a phenyl group at the indole C-2 position was tested, an inseparable mixture of indolene product 18r and indoline 16r was obtained, as well as other minor impurities (the yields quoted below are based on NMR against an internal standard). The increased stability of the doubly benzylic radical that this reaction proceeds by, as well as the fact that this radical would be expected to undergo oxidation more easily, both account for the contrasting reactivity of this substrate compared with its alkyl substituted analogues. Although this reaction is not useful synthetically, the small amount of 16r produced did appear to be formed as a single diastereoisomer, most likely with the same relative stereochemistry as that obtained for products 16b–f.


28 The structural features of 13p and 13q (the elongated tether in 13p and reduction of the carbonyl group in 13q) were designed to disrupt formation of the EDA complex that is proposed to enable charge transfer and the resulting reaction.

29 The blue LED spectral output is a bell curve centred at 455 nm, with sufficient irradiance in the 400–420 nm range to trigger slow radical initiation from substrates 13p and 13q. We believe these substrates to be competent thyl radical chain carriers, as exemplified by the fact that an increase in yield for the conversion of 13q → 16q, from 28 to 65%, was observed upon the addition of 20 mol% of ynone 13k, a substrate with a significantly higher absorance at 455 nm.


31 Unfortunately, we have been unable to obtain clear structural information on the fate of the initiator species 25 following HAT. Analysis of the unpurified reaction a typical reaction between ynone 13l and thiophenol using.
ESI mass spectrometry led to the detection of peak representing a reduced version of the starting material (ynone 13I + H₂ + H⁺), but no identifiable products could be isolated from the reaction.

32 For more details on the method used to calculate quantum yield, see ESI page S9,† and for important background on such methods, see: (a) M. A. Cismesia and T. P. Yoon, Chem. Sci., 2015, 6, 5426; (b) K. Liang, N. Li, Y. Zhang, T. Li and C. Xia, Chem. Sci., 2019, 10, 3049.

33 The proposed mechanism is further supported by deuterium labelling studies in which the reaction of ynone 13I with PhSD was performed, with the expected deuterated product (16I, see ESI, pages S12 and S13†) being obtained. No significant difference in rate of reaction was observed when comparing this reaction with the analogous reaction with PhSH, suggesting that the HAT step is not rate determining (also see ESI, pages S12 and S13†).

34 Attempts to provide additional evidence for the existence of the EDA complex using cyclic voltammetry were inconclusive (see ESI pages S15 and S16†).
