Synthetic and mechanistic studies into the rearrangement of spirocyclic indolenines into quinolines

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**Abstract:** A Density Functional Theory (DFT) approach has been used to shed light on the mechanism of a recently discovered rearrangement reaction for the conversion of spirocyclic indolenines into cyclopentanone-fused quinolines. A new base-mediated variant of this unusual rearrangement reaction has also been developed, that operates at much lower temperatures than those required in the analogous acidic reactions. The DFT study suggests that both the acid and base-mediated variants proceed via an enol/enolate intermediate and the ease with which this key intermediate forms appears to be crucial explaining in the kinetic outcomes.

Introduction

The quinoline core is of great historical1 and current2 importance in the field of heterocyclic chemistry in view of the many useful applications of quinoline-containing molecules; for example, quinolines can be found in medicines, agrochemicals, dyes, ligands, catalysts, materials and electronic devices.1-2 Consequently, many powerful methods for the synthesis of quinolines have been developed over the years.3,4 Classical named-reactions such as the Skraup, Friedlander, Doebner–von Miller, Conrad–Limbach, Combes and Pfitzinger reactions are rightly held in high regard3 and modified/improved quinoline syntheses continue to be actively developed.4

We recently reported5 a new way to access cyclopentanone-fused quinolines **2**6 from indole-tethered ynones **1** (Scheme 1a). The proposed mechanism for this one-pot process is illustrated the conversion of ynone **1a** into quinoline **2a** (Scheme 1b). First, ynone **1a** is converted into spirocyclic indolenine7 **3a** via a dearomatizing spirocyclisation reaction8,9,10upon reaction with π-acidic silver(I) triflate11 in *i*-PrOH at room temperature. Then, the addition of AlCl3·6H2O directly to this reaction mixture and heating to 100 °C in a microwave was found to promote a hitherto unprecedented rearrangement into quinoline **2a**; the rearrangement was tentatively proposed to proceed via an enolization (**3a** → **4a**), cyclopropanation (**4a** → **5a**), ring expansion (**5a** → **6a**) and tautomerization (**6a** → **3a**) cascade sequence, as shown in Scheme 1b, although it should be stressed that no evidence was obtained in support of this mechanism. Later, Van der Eycken and co-workers went on to develop a transition metal-free variant of this transformation,12,13 using trifluoracetic acid (TFA) to promote the same overall transformation, enabling a broad range of quinolines to be prepared using a simple, single step protocol that also benefitted from reduced reaction times (**7** → **8**, Scheme 1c). The authors proposed broadly the same mechanism as that shown in Scheme 1b for this metal-free variant, although again, no evidence was obtained in its support. Most recently, Song, Liu and co-workers observed a closely related transformation unexpectedly during a silver(I) catalysed trifluoromethylation cascade process and the same mechanism was again proposed.14



**Scheme 1.** Ynone to indolenine to quinoline rearrangements.

To the best of our knowledge, this indolenine to quinoline rearrangement reaction is without precedent outside of these studies.5,12,14 Therefore, we believe that more convincingly ascertaining the mechanism of this unusual ring expansion rearrangement reaction is important,15 and our attempts to do so are reported in this manuscript using a Density Functional Theory (DFT) approach.16 Additional synthetic studies performed to support the computational aspects have also led to a new base-mediated variant of this reaction being established, that operates at much lower temperatures than those used in the previous studies. The DFT results obtained support the mechanism proposed in the earlier synthetic studies and the ease with which a key enol/enolate reactive is formed appears to play a major role in explaining the surprising kinetic outcomes of the different variants.

Results and Discussion

The optimal conditions used our previous work,5a and in the Van der Eycken study,12 utilised microwave heating and reaction temperatures of 100 °C,which enabled the quinoline target molecules **2**/**8** to be prepared in high yields within 1 hour. Before embarking on the DFT study, it was decided to gauge whether such vigorous heating is strictly necessary; we reasoned that having a clearer idea of the minimum temperature required to promote rearrangement would be helpful later when interpreting the computational results. Thus, simple model spirocycle **3a** (which had already been shown in the literature to be a good substrate in both the AlCl3·6H2O and TFA promoted reaction systems,5,12 Table 1, entries 1–2) was chosen as a model system to test the limits of the rearrangement step by switching from microwave to conventional heating and lowering the temperature until the reactions begin to shut down (Table 1).

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| **Table 1.** Temperature limits for the rearrangement of spirocycle **3a** into quinoline **2a**. | | | | |
| entry | conditions | temp/°C | time/h | Conversion[a] |
| 1 | See ref 5a (AlCl3·6H2O) | 100 | 1 | 100 |
| 2 | See ref 12 (TFA) | 100 | 0.5 | 100 |
| 3 | AlCl3·6H2O (5 mol%),  *i-*PrOH, (0.1 M), heating | 80 | 24 | 100 |
| 4 | 50 | 24 | 38 |
| 5 | 40 | 24 | 0 |
| 6 | 1:1 TFA:CHCl3 (0.1 M) | 60 | 24 | 100 |
| 7 | 50 | 24 | 100 |
| 8 | 40 | 24 | 100[b] |
| 9 | RT | 24 | 54 |
| 10 | LHMDS (1 equiv.), THF (0.2 M) | RT | 0.5 | 100 |
| 11 | 0 | 0.5 | 100 |
| 12 | −20 | 1.5 | 100 |
| 13 | –46 | 3 | 58 |
| 14 | LHMDS (1 equiv.), TMEDA (2 equiv.) THF (0.2 M) | RT | 0.5 | 100 |
| [a] Conversion is based on integration of signals corresponding to **3a** and **2a** in the 1H NMR spectra of the unpurified reaction mixture. [b] All of **3a** was consumed but the product formed contained unidentified impurities. TMEDA = tetramethylethylenediamine | | | | |

Starting with the use of AlCl3·6H2O in *i*-PrOH, it was found that full conversion of spirocycle **3a** into quinoline **2a** can be still achieved at 80 °C, partial conversion (38%) is observed at 50 °C and the reactions only shut down completely when the temperature is reduced to 40 °C (Table 1, entries 3–5). Thus, the reaction is viable at much lower temperatures than those used in the published synthetic study. The same was found when examining Van der Eycken’s TFA-mediated variant; indeed, full conversion into **2a** was observed right down to 40 °C using these conditions, with partial conversion (54%) at RT.17,18 The knowledge that these reactions can be performed at lower temperatures if required is likely to be useful when more sensitive functional groups are present in the substrates.

We also decided to examine the analogous base-mediated rearrangement of **3a** into **2a** (Table 1, entries 10–13). We already knew from initial screening during our earlier work5a that lithium hexamethyldisilazide (LHMDS) can also promote this rearrangement, but this base-mediated variant was not examined in synthetic studies. Thus, we examined the conversion of **3a** into **2a** using 1 equivalent of LHMDS in THF at various temperature and found that these basic conditions promote the rearrangement at temperatures as low as –46 °C (*i.e*. much lower than either of the AlCl3·6H2O or TFA variants).



**Scheme 2.** LHMDS-mediated rearrangement of spirocycles **3a–i** into quinolines **2a–i** and **9.**



**Figure 1** DFT-calculated energies for (a) formation of **2a** from **3a** and the proposed pathway for the formation of **A** and **K** (b) ring-expansion and 1,5 hydride shifts corresponding to the base-promoted formation of **2a** from **3a**. Energies are Gibbs energies at 298 K in kJ·mol–1 at the D3BJ-PBE0/def2-TZVPP//BP86/SV(P) level with SCRF solvent correction in THF.



**Figure 2** DFT-calculated energies for ring-expansion and 1,5 hydride shifts corresponding to the base-promoted formation of **2a** from **3a**. Energies are Gibbs energies at 298 K in kJ·mol–1 at the D3BJ-PBE0/def2-TZVPP//BP86/SV(P) level with SCRF solvent correction in CHCl3.

The ability to conduct these reactions under these mild and complementary basic conditions could have useful synthetic implications. Therefore, we tested the LHMDS-mediated conditions on a range of spirocycles **3a**–**i**, and pleasingly, the expected quinolines **2a**–**I** were isolated in each case. The reaction of spirocycle **3i** is noteworthy in that alongside the expected quinoline **2i**, a minor oxidized side product **9** was also isolated; this system presumably was more prone to undergo spontaneous oxidation as result of the extra conjugation in the product.[14]

Next, the ring-expansion process (under both acidic and basic conditions) was modelled using Density Functional Theory. Geometries were optimized at the BP86/SV(P) level of theory and confirmed as minima or transition states through analysis of the calculated vibrational modes. The energies of the resulting geometries were then obtained using the hybrid PBE0 functional with the triple zeta def2-TZVPP basis set.[19] The Gibbs energies were obtained by combining these electronic energies with thermal corrections from the BP86/SV(P) level at 298 K. This method allows for an accurate description of the electronic structure of the molecule but saves on the computational expense of determining the thermal corrections at the PBE0/def2-TZVPP level. Dispersion effects were modelled with Grimme’s D3 method with Becke-Johnson dampening.[20] The effects of solvation on the reaction were modelled with an PCM model in THF (for the base-promoted reaction) and CHCl3 (acid-promoted) simulating the reaction conditions. This was the method that was previously used in our previous work on ynone cyclisations.[16]

In order to ensure that the diffusion effects of modelling an anionic pathway were being effectively captured, the surface was also calculated using the 6-311+G\* basis set with the PBE0 functional. The resulting energies show no significant differences from those at the PBE0/def2-TZVPP level (see ESI). The effect of different density functionals on the relative energies of the calculated states was also investigated. The energies of all the intermediate species showed negligible method effects. Although, when compared to the relative energies at the PBE0 functional, the transition states energies were systematically lower when BP86 was used and higher at the M06-2X and B97XD level (see ESI).

The formation of **2a** from **3a** was found to be exergonic by 91 kJ mol-1, demonstrating that, as expected, the formation of the quinoline products is thermodynamically favorable (Figure 1a). Two mechanistic pathways were then considered for this transformation as, on the basis experimental results, the reaction could be either base- or acid-promoted

Considering the base-promoted reaction first (Figure 1b). In order to model the ring-opening reaction, the most acidic protons in **3a** were considered to be those in the -position to the carbonyl group. The addition of TMEDA to sequester Li+ did not affect the outcome of the experimental reaction (Table 1 Entry 14) indicating that the cations were not playing a role in the transformation and were hence excluded from the calculations. Therefore, the starting point for the calculations was anion **A** in which the deprotonation event had already occurred: this was also taken as the reference state for the potential energy surface (Figure 1b). Compound **B** (+11 kJ mol-1) can be formed from **A** through a low-lying transition state **TSAB** (+ 19 kJ mol-1) and this process corresponds to formal nucleophilic attack by the enolate at the 2-position of the indolenine unit. Opening of the cyclopropyl group in **B** proceeds through **TSBC** (+16 kJ mol-1) to give **C** (−46 kJ mol-1) via a fragmentation reaction. Compound **C** may interconvert to **D**, **E**, **F** and **G** through a series of formal 1,5 hydride shifts. From **C**, the lowest energy 1,5 hydride shift is through **TSCD** (+33 kJ mol-1) to give the highest energy isomer of the ring-expanded annulated product compound (**D** = +8 kJ mol-1). However, the subsequent 1,5-hydride shift from **D** gives the lowest energy isomer **E** (−119 kJ mol-1) through a low-lying transition state (**TSDE**). Given that all the other transition states are higher in energy, and that **E** is the lowest energy isomer, we would expect **E** to be the dominant form in solution, which on acid work up would be protonated to give **2a**.

As an aside, based on this hydride migration mechanism, we briefly examined the effect of replacing the hydrogen atom that undergoes migration with a benzyl group that might have been expected to migrate similarly. Thus, indolenine **3j** was prepared and reacted with LHMDS in the usual way. Rearrangement into a quinoline product was indeed observed, although in this case, following the first 1,5-migration (analogous to the conversion of **C** into **D** into Figure 1) the usual sequence was interrupted, allowing tertiary alcohol quinoline derivative **10** to be isolated in 61% yield (Scheme 3).



**Scheme 3.** LHMDS-mediated rearrangement of spirocycle **3j** into quinoline **10**.

Returning to the DFT studies, we also considered the acid-promoted reaction (Figure 2). As the opening of the spirocycle operates through both Lewis and Brønsted conditions we elected to model the acid-promoted reaction by simply investigating the effects of protonation. It was considered that the indole nitrogen in **3a** would be the most basic site. Protonation of this nitrogen would give **J**, which was taken as the reference state. The isomeric form **J’**, in which protonation has occurred at the carbonyl oxygen, lies +37 kJ mol-1 higher in energy, supporting this argument that addition of H+ to the nitrogen is the thermodynamically preferred site of protonation. All attempts to find transition states which resulted in the formation of cyclopropyl derivative **L** from **J** were unsuccessful. However, it was found that **L** could be formed directly from **K** (+40 kJ mol-1), which is the enol tautomer of **J**, through **TSKL**(+46 kJ mol-1). Opening of the cyclopropyl group in **L** proceeds through **TSLM** (+60 kJ mol-1) to give **M** (+26 kJ mol-1). As was the case for the base-catalysed reaction, **M** may convert to a series of isomers through formal 1,5-hydride shifts. Isomers **N**, **O**, **P**, and **Q** are all at lower energy than **J**, with **O** being the thermodynamically preferred isomer (−64 kJ mol-1). Considering that the reaction may be performed with a large excess of TFA, the possibility of the substrate being doubly protonated cannot be discounted. However, all attempts to locate a transition state for the opening of the spirocycle from a dicationic intermediate have been unsuccessful.

Conclusions

In summary, convincing computational support has been obtained for the mechanism of rearrangement for the conversion of cyclopentenone-based spirocyclic indolenines into fused quinolines. The DFT results support the mechanisms proposed in the earlier synthetic studies and provide additional insight into the likely pathway by which the 1,5-hydride shifts operate. A base-catalyzed variant of the rearrangement has also been established that works at significantly lower temperatures than those used in the analogous acid-catalysed reactions.

The calculations demonstrate that the barriers to the opening of the spirocycle through cyclopropyl **B** (base-promoted) or **L** (acid promoted) are low. In the base-promoted case, **TSBC** lies at +16 kJ mol-1 relative to the reference state **A** which (when taken with the fact that **TSAB** lies at –19 kJ mol-1) indicates that the ring-opening process will be rapid when deprotonation has occurred. This is the case for all computational methods investigated. These data are consistent with the observation that the reaction between **3a** and LiHMDS is efficient even at –46 ºC.

In the case of the acid-promoted reaction, the energetic span for ring opening of the spirocycle (difference in energy between **J** and **TSLM**) is 60 kJ mol-1, higher than the corresponding barrier in the base-promoted case. However, the reaction generally required elevated temperatures (80 ºC) and long reaction times (24 h). The barrier of 60 kJ mol-1 would indicate that, if these states were rate controlling, then ring-opening would be complete under far less forcing conditions. However, it is important to stress that it was not possible to locate a transition state for ring opening from **J** and that tautomerization to **K** is a requirement for opening of the spirocycle.The conversion of **J** to **K** is almost certainly a bimolecular process and, as the nature of such an intermolecular deprotonation/re-protonation is complex, this step was not modelled. However, our data indicate that it is this process which is controlling the reaction rather than the C–C bond migration needed to open the spirocycle. As such, slow enol formation (under acidic conditions) in contrast with rapid enolate formation when using strong base is likely the key contributing factor to the stark difference in rate of the two processes.

Experimental Section

**General Procedure A: AlCl3 Temperature Screens**

To a microwave vial containing a solution of spirocycle (0.3 mmol) in *iso*-propanol (3 mL), was added AlCl3·6H2O (15 µmol). The reaction mixture was heated at the desired temperature for 24 hours. After this time, an aliquot was taken and concentrated *in vacuo* and a 1H NMR spectrum was recorded in CDCl3 to analyse the percentage conversion.

**General Procedure B: TFA Temperature Screens**

To a microwave vial containing a solution of spirocycle (0.3 mmol) in chloroform (1.5 mL) was added TFA (1.5 mL, 20 mmol). The reaction mixture was heated at the desired temperature for 24 hours. After this time, an aliquot was taken and concentrated *in vacuo* and a 1H NMR spectrum was recorded in CDCl3 to analyse the percentage conversion.

**General Procedure C: LHMDS Temperature Screens**

To a solution of spirocycle (0.75 mmol) in THF (3.75 mL), at −78 °C under an atmosphere of argon, was added LHMDS (0.75 mL, 0.75 mmol, 1 M in THF). The solution was stirred for 5 min, then warmed to the desired temperature with continued stirring, frequently checking for completion by TLC analysis. The reaction was quenched with sat. aq. NH4Cl (5 mL), diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined and dried over MgSO4, concentrated *in vacuo.* A 1H NMR spectrum was recorded in CDCl3 to analyse the percentage conversion.

**General Procedure D: LHMDS Mediated Rearrangement**

To a solution of spirocycle (0.5 mmol) in THF (2.5 mL), at −78 °C under an atmosphere of argon, was added LHMDS (0.6 mL, 0.6 mmol, 1.0 M in THF). The solution was stirred for 5 min at −78 °C and then warmed to RT. The reaction mixture was stirred at RT until TLC analysis showed the reaction had gone to completion. The reaction was quenched with sat. aq. NH4Cl (5 mL), diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined and dried over MgSO4, concentrated *in vacuo* and purified by flash column chromatography to afford the quinoline product.

**1-Phenyl-1,2-dihydro-3*H*-cyclopenta[c]quinolin-3-one (2a):** Synthesised using general procedure D (30 minutes reaction time) from 2-phenylspiro[cyclopent[2]ene-1,3'-indol]-4-one **3a** (194 mg, 0.75 mmol). Purification by flash column chromatography (4:1 to 1:1 hexane/EtOAc) afforded the *titled product* **2a** as a pale brown solid (157 mg, 81%). *R*f = 0.51 (hexane/EtOAc 1:1); 1H NMR (400 MHz, CDCl3): δ = 9.32 (s, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.82 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.73 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.49 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.36 – 7.25 (m, 3H), 7.16 – 7.12 (m, 2H), 5.05 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.42 (dd, *J* = 19.0, 8.0 Hz, 1H), 2.78 ppm (dd, *J* = 19.0, 3.0 Hz, 1H). Spectroscopic data matched those reported in the literature.5

**LHMDS-Mediated Rearrangement of 3a with TMEDA**

To a solution of 2-phenylspiro[cyclopent[2]ene-1,3'-indol]-4-one **3a** (77 mg, 0.3 mmol) and distilled TMEDA (0.1 mL, 0.6 mmol) in THF (1.5 mL), at −78 °C under an atmosphere of argon, was added LHMDS (0.3 mL, 0.3 mmol, 1 M in THF). The solution was stirred for 5 min, then warmed to room temperature with continued stirring for 30 minutes. The reaction was quenched with sat. aq. NH4Cl (10 mL), diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined, washed with sat. aq. NaCl (10 mL), dried over MgSO4 and concentrated in vacuo. A 1H NMR spectrum was recorded in CDCl3 to analyse the reaction mixture and this confirmed that ynone **3a** was fully and cleanly converted into quinoline **2a**, as was the case in the analogous reaction without TMEDA.

**1-(4-Methoxyphenyl)-1,2-dihydro-3*H*-cyclopenta[c]quinolin-3-one (2b):** Synthesised using general procedure D (30 minutes reaction time) from 2-(4-methoxyphenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-one **3b** (145 mg, 0.5 mmol). Purification by flash column chromatography (1:1 hexane/EtOAc) afforded the *titled product* **2b** as an orange solid (133 mg, 92%). *R*f = 0.39 (hexane/EtOAc 1:1); 1H NMR (400 MHz, CDCl3): δ = 9.27 (s, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.80 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.73 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.47 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.04 – 6.99 (m, 2H), 6.84 – 6.80 (m, 2H), 4.99 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.76 (s, 3H), 3.37 (dd, *J* = 19.0, 8.0 Hz, 1H), 2.72 ppm (dd, *J* = 19.0, 3.0 Hz, 1H). Spectroscopic data matched those reported in the literature.5

**1-(4-Fluorophenyl)-1,2-dihydro-3*H*-cyclopenta[c]quinolin-3-one (2c):** Synthesised using general procedure D (30 minutes reaction time) from 2-(4-fluorophenyl)spiro[cyclopent[2]ene-1,3'-indol]-4-one **3c** (139 mg, 0.5 mmol). Purification by flash column chromatography (1:1 hexane/EtOAc) afforded the *titled product* **2c** as an orange solid (99 mg, 71%). *R*f = 0.45 (hexane/EtOAc 1:1); 1H NMR (400 MHz, CDCl3): δ = 9.31 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.85 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.68 (ddd, *J* = 8.5, 1.5, 0.5 Hz, 1H), 7.50 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.11 – 7.05 (m, 2H), 7.04 – 6.97 (m, 2H), 5.04 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.41 (dd, *J* = 19.5, 8.0 Hz, 1H), 2.73 ppm (dd, *J* = 19.5, 3.0 Hz, 1H). 19F NMR (376 MHz, CDCl3): δ = -114.5 ppm. Spectroscopic data matched those reported in the literature.12

**1-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1,2-dihydro-3*H*-cyclopenta[c]quinolin-3-one (2d):** Synthesised using general procedure D (1 hour reaction time) from 2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)spiro[cyclopentane-1,3'-indol]-2-en-4-one **3d** (103 mg, 0.3 mmol). Purification by flash column chromatography (4:1 to 7:3 hexane/EtOAc) afforded the *titled product* **2d** as a brown oil (60 mg, 59%). *R*f = 0.33 (hexane/EtOAc 7:3); 1H NMR (400 MHz, CDCl3): δ = 9.15 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.87 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.68 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 4.15 – 4.08 (m, 1H), 3.82 (dt, *J* = 10.5, 4.5 Hz, 1H), 3.71 (td, *J* = 10.5, 4.5 Hz, 1H), 2.98 (dd, *J* = 19.0, 7.5 Hz, 1H), 2.67 (dd, *J* = 19.0, 1.5 Hz, 1H), 2.49 – 2.41 (m, 1H), 1.63 (tdd, *J* = 14.0, 10.0, 4.5 Hz, 1H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 ppm (s, 3H). Spectroscopic data matched those reported in the literature.5

**4-Methyl-1-phenyl-1,2-dihydro-3*H*-cyclopenta[c]quinolin-3-one (2e):** Synthesised using general procedure D (1.5 hour reaction time) from 2-phenyl-2'-methylspiro[cyclopent[2]ene-1,3'-indol]-4-one **3e** (137 mg, 0.5 mmol). Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the *titled product* **2e** as an orange solid (97 mg, 71%). *R*f = 0.48 (hexane/EtOAc 1:1); 1H NMR (400 MHz, CDCl3): δ = 8.11 (d, *J* = 8.5 Hz, 1H), 7.77 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.5, 1.5, 0.5 Hz, 1H), 7.39 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.33 – 7.25 (m, 3H), 7.13 – 7.09 (m, 2H), 4.98 (dd, *J* = 7.5, 2.5 Hz, 1H), 3.38 (dd, *J* = 19.0, 7.5 Hz, 1H), 3.06 (s, 3H), 2.75 ppm (dd, J = 19.0, 2.5 Hz, 1H). Spectroscopic data matched those reported in the literature.12

**1-Butyl-4-methyl-1,2-dihydro-3*H*-cyclopenta[c]quinolin-3-one (2f):** Synthesised using general procedure D (1 hour reaction time) from 2-butyl-2’-methylspiro[cyclopent[2]ene-1,3'-indol]-4-one **3f** (127 mg, 0.5 mmol). Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the *titled product* **2f** as a yellow solid (76 mg, 60%). *R*f = 0.31 (hexane/EtOAc 7:3); m.p. 88 – 89 °C; 1H NMR (400 MHz, CDCl3): δ = 8.11 (d, *J* = 8.5 Hz, 1H), 8.04 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.83 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.60 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 3.87 – 3.78 (m, 1H), 2.95 (s, 3H), 2.94 (dd, *J* = 19.0, 7.0 Hz, 1H), 2.59 (dd, *J* = 19.0, 1.5 Hz, 1H), 2.19 – 2.02 (m, 1H), 1.57 – 1.20 (m, 5H), 0.89 ppm (t, *J* = 6.5 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ = 205.5 (C=O), 169.0 (C), 157.4 (C), 149.7 (C), 132.4 (CH), 129.9 (CH), 128.1 (C), 126.6 (CH), 124.4 (C), 124.4 (CH), 43.8 (CH2), 36.9 (C), 36.2 (CH2), 29.8 (CH2), 22.8 (CH3), 22.7 (CH2), 14.1 ppm (CH3); IR (thin film): νmax = 1708 (s, C=O), 1616 (C=C), 1588 (C=C) cm-1; HRMS (ESI): *m*/*z* calcd for C17H20NONa+: 254.1539 [*M*+Na]+; found: 254.1538.

**8-Bromo-1-phenyl-1,2-dihydro-3*H*-cyclopenta[c]quinolin-3-one (2g):** Synthesised using general procedure D (30 minutes reaction time) from 5'-bromo-2-phenylspiro[cyclopent[2]ene-1,3'-indol]-4-one **3g** (169 mg, 0.5 mmol). Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the *titled product* **2g** as a yellow solid (136 mg, 80%). *R*f = 0.39 (hexane/EtOAc 7:3); 1H NMR (400 MHz, CDCl3): δ = 9.30 (s, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 7.87 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.12 – 7.09 (m, 2H), 4.99 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.41 (dd, *J* = 19.5, 8.0 Hz, 1H), 2.79 ppm (dd, *J* = 19.5, 3.0 Hz, 1H). Spectroscopic data matched those reported in the literature.12

***trans*-2-(4-Methylphenyl)-1-phenyl-1,2-dihydro-3*H*-cyclopenta[c]quinolin-3-one (2i):** Synthesised using general procedure D (2.5 hour reaction time) from 3-(4-methylphenyl)-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-4-one **3i** (175 mg, 0.5 mmol). Purification by flash column chromatography (9:1 to 3:1 hexane/EtOAc) afforded the *titled product* **2i** as an orange oil (105 mg, 60%). *R*f = 0.33 (hexane/EtOAc 3:1); 1H NMR (400 MHz, CDCl3): δ = 9.37 (s, 1H), 8.27 (br. d, *J* = 8.5 Hz, 1H), 7.82 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.65 (ddd, *J* = 8.5, 1.5, 0.5 Hz, 1H), 7.45 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.34 – 7.28 (m, 3H), 7.17 – 7.13 (m, 2H), 7.09 – 7.05 (m, 2H), 7.03 – 6.99 (m, 2H), 4.99 (d, *J* = 3.5 Hz, 1H), 3.87 (d, *J* = 3.5 Hz, 1H), 2.34 ppm (s, 3H); 13C NMR (100 MHz, CDCl3): δ = 204.0 (C), 164.2 (C), 151.1 (C), 146.0 (CH), 141.9 (C), 137.3 (C), 135.2 (C), 132.5 (CH), 130.7 (CH), 129.8 (CH), 129.7 (C), 129.4 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 125.9 (CH), 125.2 (C), 65.0 (CH), 54.4 (CH), 21.2 ppm (CH3); IR (thin film): νmax = 1714 (s, C=O), 1615 (C=C), 1574 (C=C) cm-1; HRMS (ESI): *m*/*z* calcd for C25H19NONa+: 372.1539 [*M*+Na]+; found: 372.1351.

**2-(4-Methylphenyl)-1-phenyl-cyclopenta[c]quinoline-3-one (9):** Side product formed from the reaction of 3-(4-methylphenyl)-2-phenylspiro[cyclopentane-1,3‘-indol]-2-en-4-one **3i** using general procedure D. Purification by flash column chromatography (9:1 to 3:1 hexane/EtOAc) afforded the *titled product* **9** as a red solid (36 mg, 20%). *R*f = 0.40 (hexane/EtOAc 3:1); m.p. 183 – 187 °C; 1H NMR (400 MHz, CDCl3): δ = 9.05 (s, 1H), 8.09 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.68 (ddd, *J* = 8.5, 4.5, 4.0 Hz, 1H), 7.55 – 7.49 (m, 3H), 7.46 – 7.40 (m, 2H), 7.26 – 7.22 (m, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 2.31 ppm (s, 3H); 13C NMR (100 MHz, CDCl3): δ = 197.0 (C), 153.8 (C), 153.2 (C), 153.2 (C), 142.9 (CH), 138.7 (C), 134.9 (C), 134.2 (C), 131. 8 (CH), 130.8 (CH), 130.2 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 128.7 (CH), 127.3 (CH), 126.9 (C), 125.3 (CH), 122.9 (C), 119.9 (C), 21.5 ppm (CH3); IR (thin film): νmax = 1707 (s, C=O), 1618 (C=C), 1562 (C=C) cm-1; HRMS (ESI): *m*/*z* calcd for C25H18NO+: 348.1383 [*M*+H]+; found: 348.1377.

**3-Benzyl-1-phenylcyclopenta[c]quinolin-3-ol (10):** Synthesised using general procedure D (1 hour reaction time) from a 1:1 mixture of diastereoisomers of 5-benzyl-2-phenylspiro[cyclopentane-1,3'-indol]-2-en-4-one **3j** (175 mg, 0.5 mmol). Purification by flash column chromatography (6:4 hexane/EtOAc) afforded the *titled product* **10** as an orange solid (106 mg, 61%). *R*f = 0.13 (hexane/EtOAc 6:4); m.p. 191 – 192 °C; 1H NMR (400 MHz, (CD3)2SO): δ = 8.93 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.60 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.35 – 7.20 (m, 4H), 7.11 – 7.02 (m, 5H), 6.50, (s, 1H), 5.93 ppm (s, 1H); 13C NMR (100 MHz, (CD3)2SO): δ = 148.7 (C), 145.5 (CH), 145.1 (CH), 144.8 (C), 142.2 (C), 141.3 (C), 136.6 (C), 136.4 (C), 130.2 (CH), 129.9 (CH), 128.6 (CH), 128.6 (CH), 128.2 (CH), 128.2 (CH), 127.3 (CH), 126.2 (CH), 125.9 (CH), 123.5 (CH), 122.7 (C), 82.8 (C), 43.7 ppm (CH2); IR (thin film): νmax = 1569 (C=C), 1506 (C=C) cm-1; HRMS (ESI): *m*/*z* calcd for C25H20NO+: 350.1539 [*M*+H]+; found: 350.1539. Note: In (CD3)2SO some proton signals are obscured by the residual water signal; these are observed in CDCl3 at 3.45 (d, *J* = 13.5 Hz, 1H) and 3.30 (d, *J* = 13.5 Hz, 1H) for the CH2 of the benzyl group.

**1-Butyl-2-(4-methylphenyl)-4-methyl-1,2-dihydro-3H-cyclopenta[c]quinolin-3-one (2h):** Synthesised using general procedure D from 2-butyl-3-(4-methylphenyl)-2’-methylspiro[cyclopentane-1,3'-indol]-2-en-4-one **3h** (165 mg, 0.5 mmol). Purification by flash column chromatography (99:1 to 95:5 hexane/acetone) afforded the *titled product* **2h** as an orange oil as a 7:3 mixture of diastereoisomers (98 mg, 58%). *R*f = 0.08 (hexane/acetone 95:5); 1H NMR (400 MHz, CDCl3): δ = 8.19 – 8.14 (m, 2H), 8.12 – 8.04 (m, 2H), 7.92 – 7.84 (m, 2H), 7.67 – 7.60 (m, 2H), 7.25 – 7.19 (m, 4H), 7.14 – 7.08 (m, 2H), 7.05 – 6.99 (m, 2H), 4.25 (d, *J* = 7.0 Hz, 1H), 4.15 (m, 1 H), 3.91 (ddd, *J* = 9.5, 3.0, 1.5 Hz; 1H), 3.71 (d, *J* = 1.5 Hz, 1H), 3.04 (s, 3H), 2.96 (3H), 2.33 (s, 3H), 2.30 (s, 3H), 2.25 – 2.17 (m, 1H), 1.68 – 1.27 (m, 8H), 1.03 – 0.81 (m, 2H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.60 – 0.48 (m, 1H), 0.57 ppm (t, *J* = 6.5 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ = 205.0 (C), 204.7 (C), 168.6 (C), 166.9 (C), 158.1 (C), 157.5 (C), 149.9 (C), 149.7 (C), 139.3 (C), 137.1 (C), 136.6 (C), 136.4(C), 132.7 (CH), 132.6 (C), 132.5 (CH), 130.4 (CH), 130.0 (CH), 129.9 (CH), 129.8 (CH), 129.4 (C), 129.3 (CH), 127.8 (C), 127.3 (CH), 126.8 (CH), 126.7 (CH), 125.0 (C), 124.5 (CH), 124.3 (CH), 60.7 (CH), 59.3 (CH), 46.6 (CH), 42.8 (CH), 36.5 (CH2), 33.1 (CH2), 30.0 (CH2), 29.5 (CH2), 22.9 (CH3), 22.8 (CH2), 22.8 (CH3), 22.6 (CH2), 21.3 (CH3), 21.2 (CH3), 14.1 (CH3), 13.7 ppm (CH3); IR (thin film): νmax = 1710 (s, C=O), 1615 (C=C), 1590 (C=C), 1565 (C=C), 1512 (C=C); HRMS (ESI): *m*/*z* calcd for C24H25NONa+: 366.1828 [*M*+Na]+; found: 366.1821

**1-(2-Methyl-1*H*-indol-3-yl)oct-3-yn-2-one:** To a solution of hex-1-yne (1.2 mL, 10.5 mmol) in THF (10.5 mL), at −78 °C under an atmosphere of argon, was added *n*-BuLi (5.5 mL, 8.8 mmol, 1.6 M in hexane). The mixture was stirred for 30 min at −78 °C then transferred via cannula to a solution of *N*-methoxy-*N*-methyl-2-(2-methyl-1*H*-indol-3-yl)acetamide (813 mg, 3.5 mmol) in THF (17.5 mL) which was also cooled to −78 °C under an atmosphere of argon. The resulting mixture was stirred for 5 min and then warmed to RT with continued stirring for 1 hr. The reaction was quenched with sat. aq. NH4Cl (20 mL), diluted with water (10 mL) and extracted with EtOAc (3 x 30 mL). The organics were combined and dried over MgSO4, concentrated *in vacuo* and purified by flash column chromatography (9:1 to 4:1 hexane/EtOAc) to afford the *titled product* **S1** as a yellow oil (414 mg, 47%). *R*f = 0.81 (hexane/EtOAc 1:1); 1H NMR (400 MHz, CDCl3): δ = 7.92 (br. s, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.16 – 7.07 (m, 2H), 3.87 (s, 2H), 2.42 (s, 3H), 2.25 (t, *J* = 7.0 Hz, 2H), 1.45 – 1.37 (m, 2H), 1.33 – 1.22 (m, 2H), 0.85 ppm (t, *J* = 7.0 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ = 185.6 (C), 135.3 (C), 133.3 (C), 128.8 (C), 121.5 (CH), 119.8 (CH), 118.3 (CH), 110.4 (CH), 103.9 (C), 95.4 (C), 81.1 (C), 41.4 (CH2), 29.6 (CH2), 21.9 (CH2), 18.8 (CH2), 13.6 (CH3), 12.0 ppm (CH3); IR (thin film): νmax = 2210 (C≡C), 1664 (C=O) cm-1; HRMS (ESI): *m*/*z* calcd for C17H19NONa+: 276.1359 [*M*+Na]+; found: 276.1363.

**2-Butyl-2‘-methylspiro[cyclopent[2]ene-1,3‘-indol]4-one (3f):** To a solution of 1-(2-methyl-1*H*-indol-3-yl)oct-3-yn-2-one (414 mg, 1.6 mmol) in DCM (16 mL) was added AgOTf (4.2 mg, 16 µmol) at RT. The reaction mixture was stirred for 1 hr and then concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane/EtOAc) afforded the *titled product* **3f** as a yellow oil (270 mg, 55%). *R*f = 0.36 (hexane/EtOAc 1:1); 1H NMR (400 MHz, CDCl3): δ = 7.57 (d, *J* = 7.5 Hz, 1H), 7.37 (ddd, *J* = 7.5, 1.5, 1.5 Hz, 1H), 7.22 (ddd, *J* = 7.5, 1.0, 1.0 Hz, 1H), 7.13 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H), 6.30 (t, *J* = 1.5 Hz, 1H), 2.72 (d, *J* = 18.5 Hz, 1H), 2.67 (d, *J* = 18.5 Hz, 1H), 2.17 (s, 3H), 1.71 – 1.53 (m, 2H), 1.41 – 1.31 (m, 2H), 1.15 (sext., *J* = 7.0 Hz, 2H), 0.76 ppm (t, *J* = 7.0 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ = 206.1 (C), 181.7 (C), 181.6 (C), 155.4 (C), 140.2 (C), 131.0 (CH), 129.0 (CH), 126.3 (CH), 121.8 (CH), 120.5 (CH), 68.6 (C), 42.7 (CH2), 29.0 (CH2), 28.2 (CH2), 22.2 (CH2), 15.5 (CH3), 13.7 ppm (CH3); IR (thin film): νmax = 1717 (s, C=O), 1693 (C=C), 1609 (C=C) cm-1; HRMS (ESI): *m*/*z* calcd for C17H19NONa+: 276.1359 [*M*+Na]+; found: 276.1361.

**2-Butyl-5-(4-methylphenyl)-2’methylspiro[cyclopentane-1,2‘-indol]-2-en-4-one (3h):** To a dry round-bottomed flask, 1-(2-methyl-1*H*-indol-3-yl)oct-3-yn-2-one **S1** (529 mg, 2.1 mmol), 4-iodotoluene (501 mg, 2.3 mmol) and bromobis(triphenylphosphine)(*N*-succinimide)palladium(II) (32 mg, 40 µmol) were added. The flask was purged with argon and then dry acetonitrile (20 mL) and triethylamine (0.3 mL, 2.1 mmol) were added. The reaction was heated to 60 °C with continuous stirring for 4 hrs. The mixture was then cooled to RT and concentrated *in vacuo*. Purification by flash column chromatography (9:1 to 7:3 hexane/EtOAc) afforded the *titled product* **3h** as a pale yellow oil (489 mg, 71%). *R*f = 0.22 (hexane/EtOAc 7:3); 1H NMR (400 MHz, CDCl3): δ = 7.63 (d, *J* = 7.5 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.29 – 7.22 (m, 6H), 2.86 (d, *J* = 19.0 Hz, 1H), 2.81 (d, *J* = 19.0 Hz, 1H), 2.39 (s, 3H), 2.27 (s, 3H), 2.05 – 1.95 (m, 1H), 1.88 – 1.78 (m, 1H), 1.06 – 0.85 (m, 4H), 0.56 ppm (t, *J* = 6.0 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ = 204.8 (C), 182.6 (C), 173.4 (C), 155.6 (C), 143.2 (C), 140.6 (C), 138.3 (C), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.3 (C), 126.1 (CH), 122.3 (CH), 120.5 (CH), 67.1 (C), 42.7 (CH2), 30.0 (CH2), 28.3 (CH3), 22.8 (CH2), 21.4 (CH3), 15.9 (CH3), 13.3 ppm (CH3); IR (thin film): νmax = 1706 (s, C=O), 1609 (C=C), 1578 (C=C) cm-1; HRMS (ESI): *m*/*z* calcd for C24H25NONa+: 366.1828 [*M*+Na]+; found: 366.1825

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[16] For other DFT studies, including information on related reaction systems, by the Unsworth and Lynam groups, see: (a) A. K. Clarke, J. M. Lynam, R. J. K. Taylor, W. P. Unsworth, *ACS Catal*. **2018**, *8*, 6844–6850; (b) J. T. R. Liddon, J. A. Rossi-Ashton, A. K. Clarke, J. M. Lynam, R. J. K. Taylor, W. P. Unsworth, *Synthesis* **2018**, *24*, 4829–4836; (c) A. Lawer, J. A. Rossi-Ashton, T. C. Stephens, B. J. Challis, R. G. Epton, J. M Lynam, W. P. Unsworth, *Angew. Chem., Int. Ed*. **2019**, DOI: 10.1002/anie.201907206

[17] Van der Eycken and co-workers also showed that partial formation of **2a** is possible at RT but settled on higher temperatures for their optimal synthetic procedure, see reference 12.

[18] Note that the work-up/purification of the TFA-mediated reactions is typically more straightforward than those using AlCl3·6H2O (in which precipitate formation can sometimes complicate isolation of the product).

[19] F. Weigend, M. Häser, H. Patzelt and R. Ahlrichs, *Chem. Phys. Lett*., **1998**, *294*, 143.

[20] S. Grimme, S. Ehrlich and L. Goerigk, *J. Comp. Chem*., **2011**, *32*, 1456-65.

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| A Density Functional Theory approach has been used to shed light on the mechanism of a recently discovered rearrangement reaction for the conversion of spirocyclic indolenines into cyclopentanone-fused quinolines. A new base-mediated variant of this unusual rearrangement reaction has also been developed, that operates at much lower temperatures than those required in the analogous acidic reactions. |  | Rearrangements  Ryan G. Epton, Aimee K. Clarke, Richard J. K. Taylor, William P. Unsworth\* and Jason M. Lynam\*  Page No. – Page No.  Synthetic and mechanistic studies into the rearrangement of spirocyclic indolenines into quinolines |
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