

Discovery of an imidazo-phenanthridine synthon produced in a 'five-step one-pot reaction' leading to a new family of heterocycles with novel physical properties†

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A new class of heterocyclic aromatic cation with novel physical properties has been constructed by an unprecedented reaction pathway that proceeds *via* five spontaneous steps to yield a 'synthon' that can be further derivatised by a final nucleophilic substitution step.

Explorations in heterocyclic chemistry are exciting because of the potential of discovering an almost unlimited resource of novel compounds with diverse physical, chemical, and biological properties.¹ Heteroaromatic templates are therefore commonly used in medicinal chemistry for the design of biologically active agents.² In this respect, the imidazole framework is a particularly important subset, widely implicated in biochemical processes.^{3–5} Indeed, the imidazolyl moiety is ubiquitous in many biologically active compounds, and has a rich chemistry which makes it an interesting building block in drug discovery.^{4,6} Furthermore, due to the possible formation of stable *N*-heterocyclic carbenes,⁷ the imidazole moiety has found wide-ranging applications in organometallic catalysis,⁸ coordination chemistry⁹ and asymmetric catalysis.¹⁰ It is not surprising that an ever increasing amount of research has focused on the improvement of the preparation and functionalisation of the imidazole moiety, notably for its fusion onto pre-existing *N*-heteroaromatic systems.^{11–14} However, all previously reported synthetic routes require the alpha position of the *N*-heterocycle to be functionalised at some point by an amino-based group (Fig. 1), which is often difficult to achieve as it requires harsh reaction conditions, such as those found in the Chichibabin reaction, or regio-selective halogenation followed by nucleophilic substitution with ammonia.¹⁵

Recently, we have developed a one-pot reaction leading to Dihydro-Imidazo-Phenanthridinium derivatives (DIPs; Scheme 1),¹⁶ a new class of heteroaromatic compound with high cytotoxicity in cancer cell lines.¹⁷ As the biological

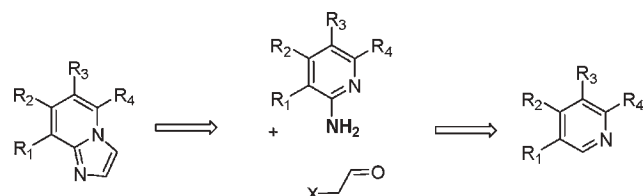


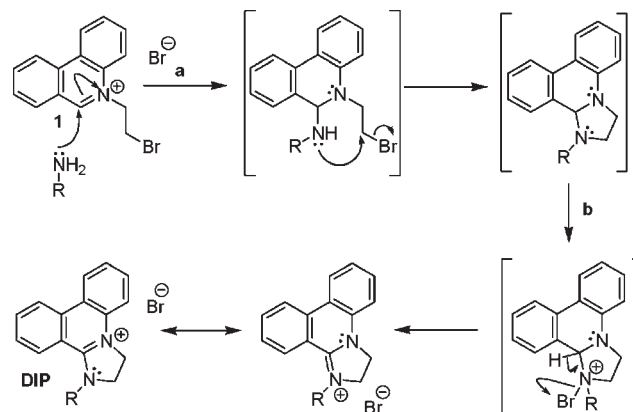
Fig. 1 A retrosynthetic approach for fused imidazole moieties.

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properties of the DIP framework are likely to come from upstream DNA intercalation,¹⁷ the development of a methodology leading to a more planar Imidazo-Phenanthridinium framework (IP; Fig. 2) was very appealing since, not only will it lead to a new family of imidazole-containing molecules, but also potentially bind more strongly to DNA due to more favourable π - π interactions. Moreover, the introduction of the imidazole moiety would open up new possibilities for tuning the DNA intercalating platform, notably *via* substitution at C₁ and C₂ (Fig. 2),¹⁸ which is harder to modify in the case of DIPs. Herein, we report a simple and efficient procedure leading to IPs from an imidazole-based intermediate obtained in an unprecedented five-step one-pot reaction.

This procedure builds upon our previous work, in which we demonstrated that the formation of the DIP derivatives occurs *via* addition of a primary amine to the highly reactive iminium moiety of starting material 2-bromoethyl-phenanthridinium bromide **1**, followed by a five-membered ring cyclisation and an oxidation step (Scheme 1).^{16,19}



Scheme 1 Reported mechanism for the formation of DIPs. Reaction conditions: a) H₂O/EtAc, NaHCO₃, 0 °C to r.t., N₂, 2 h; b) aqueous wash, NBS, 0 °C to r.t., 2 h.

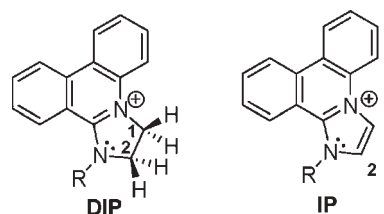
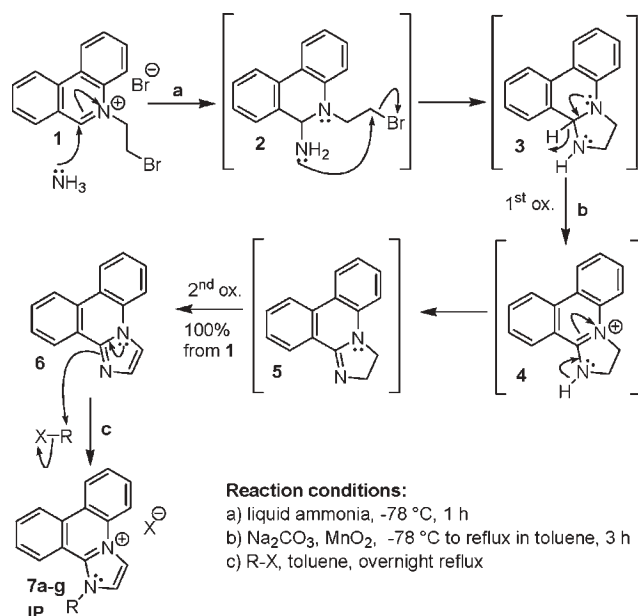


Fig. 2 Representations of the DIP and IP framework.



Scheme 2 Synthesis of platform molecule imidazo-phenanthridine **6**, and imidazo-phenanthridiniums **7a–g** (IPs).

The oxidation step which occurs during the final step of the synthesis of the **DIP** molecules occurs readily due to the high driving force which originates from the re-aromatisation of the central ring (Scheme 1). Subsequent oxidation could not transform the **DIPs** into the corresponding targeted **IPs** (Fig. 2) by using conventional oxidizing agents,[‡] probably due to the high stability of the fully aromatic **DIP** ring.¹ However, the use of ammonia as a nucleophile means that this aromaticity can be removed simply by deprotonation giving a route to form the imidazole ring from a less stable intermediate, see Scheme 2.

Herein we show that when the starting material, 2-bromoethyl-phenanthridinium bromide **1**, is reacted with liquid ammonia it then forms alpha adduct **2** which subsequently forms the imidazolidine intermediate **3** via an intramolecular cyclisation (Scheme 2). Addition of an excess of manganese dioxide under basic reaction conditions gives rise to the two necessary oxidation steps required to obtain the imidazo-phenanthridine intermediate **6** in quantitative yield. This possibly proceeds via the formation of the acidic dihydro-imidazo-phenanthridinium intermediate **4**,¹⁶ which is deprotonated *in-situ* to form the dihydro-imidazo-phenanthridine intermediate **5**. As a result, the migration of the iminium double bond during the deprotonation of **4** removes the aromaticity of the phenanthridinium moiety and provides a high driving force for the re-aromatisation and transformation of the dihydro-imidazole moiety of **5** into the imidazole moiety present in **6**.

Subsequent nucleophilic substitution of a range of electrophiles RX by the imidazo-phenanthridine **6** gives rise to a family of **IP** derivatives **7a–g** with high yield (Scheme 2 and Table 1). The last step is particularly effective as it proceeds concurrently with increased aromaticity. Precipitation of the cationic products **7a–g** from toluene during the reaction allows simple recovery by filtration. Therefore, a large excess of the electrophilic reagent can be used to drive the reaction to completion as the remaining unreacted material stays in solution.

Note that the nature of the counter-ion formed during the synthesis of the **IP** derivatives **7a–g** (Scheme 2 and Table 1) is

Table 1 Products and yields

IP #	R	X	Yield (%)
7a	R = -H;	X = Br	85
7b	R = -(CH ₂) ₃ -CH ₃ ;	X = Br	83
7c	R = -benzyl;	X = Br	90
7d	R = <i>p</i> -methoxy-benzyl;	X = Br	98
7e	R = -benzyl;	X = Cl	81
7f	R = -CH ₃ ;	X = I	95
7g	R = -CH ₃ ;	X = tosylate	99

dictated by the choice of the leaving groups used in the last nucleophilic substitution step (Scheme 2). This is useful from the drug discovery point of view since it is possible to produce a diverse library of water-soluble compounds, by judicious choice of the electrophilic reagent (See **7c** and **7e**, or **7f** and **7g**). The presence of the intermediate **3**, **5** and **6** (see supplementary information) was confirmed using mass spectrometry, and is in accordance with the proposed mechanism shown in Scheme 2. The crystal structure of compound **6** provides definitive proof for the formation of the imidazole moiety (Fig. 3). Furthermore, the imidazo derivative **6** was obtained as a light yellow powder, which turned to blue in solution after being left in the presence of sunlight for over 12 hours, which might be caused by the presence of a stable radical species.²⁰ Detailed study of this photochromic process (which is *not* shown by the **DIP** family of molecules) is underway. Structural analysis of **6** demonstrates unambiguously the delocalised nature of the formal -C=C- moiety into the five-membered ring and into the central aromatic core (C-C and C-N bond lengths in the five-membered ring range from 1.360–1.385 Å in **IP** cf. 1.331–1.521 Å in **DIP**).¹⁷ Also, compound **6** can be seen to aggregate via a range of C-H...π and π-π interactions in the solid state, see Fig. 3. Therefore, this additional planarity and extended electron delocalisation should give rise to an improvement in the DNA binding affinity of **IP** vs. **DIP**, and this indeed was observed, see Table 2.

To evaluate the DNA binding affinity of the **IP** framework, ITC experiments were carried out in a PIPES buffer of **7b–d**. Binding constants in the region of 10⁴–10⁵ M⁻¹ have been observed, which are higher than the corresponding **DIP** analogues (Table 2).

In conclusion, we have developed an unprecedented one-pot reaction yielding a key intermediate imidazo-phenanthridine (compound **6**) simply and efficiently, using only a filtration

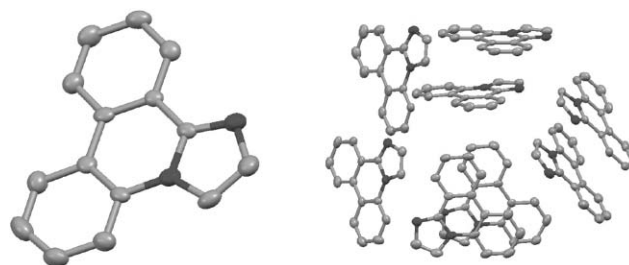
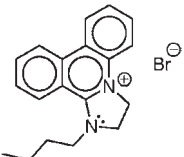
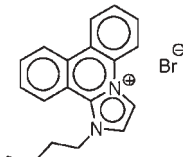
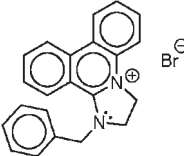
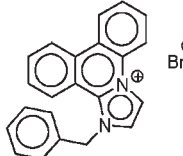
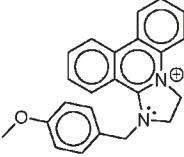
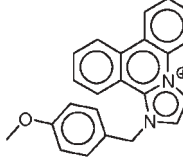


Fig. 3 LHS: ORTEP representation (30% probability ellipsoids) of the molecular structure of the synthon imidazo-phenanthridine **6**. RHS: Packed array of **6** showing π·π stacking in the solid state.

Table 2 DNA affinity of **DIP** (LHS) versus the corresponding **IP** structure (RHS)

DIP structure	Binding constants ^a ; K (M^{-1}) $\times 10^4$	Corresponding IP structure	Binding constants ^a ; K (M^{-1}) $\times 10^4$
	3.50 \pm 0.14		5.28 \pm 0.19
	4.50 \pm 0.15		6.11 \pm 0.40
	2.90 \pm 0.11		11.8 \pm 0.10

^a Salmon testes DNA.

procedure to obtain the analytically pure product. This provides a new route for the flexible synthesis of a new class of heterocycles with novel physical properties arising from the increased planarity and electron delocalisation over the entire heterocyclic framework. The improved planarity can be shown by the DNA binding affinity, compared to our Dihydro-Imidazo-Phenanthridinium derivatives (**DIPs**).¹⁷ The application of this one-pot reaction to other *N*-heteroaromatic systems is presently under investigation, as well as the development of an **IP**-library, with a particular view to examine chiral and phase transfer systems. In addition, electrochemical and photolysis studies are underway to examine the possibility of using **DIP** and **IP** to generate stable radical species.

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Notes and references

‡ In an attempt to oxidize **DIPs** to **IPs** (Fig. 2), oxidizing agents such as MnO_2 , $KMnO_4$, DDQ, H_2O_2 , H_2SO_4 and HNO_3 had been tried with a range of different solvents at different temperatures, without success.

§ **Crystallographic data 6**: $[C_{15}H_{10}N_2]$, Mr = 218.25 g mol⁻¹; colourless rod (0.50 \times 0.50 \times 0.25 mm) was analyzed with a Bruker Nonius Advance diffractometer equipped with an APEX II CCD detector using Mo-K α radiation (λ = 0.71073 Å) at 100(2) K. Monoclinic, space group $P2_1$ (no. 4), a = 11.4915(11), b = 12.2167(12), c = 16.0434(15) Å, β = 108.288(5)°, V = 2138.5(4) Å³, Z = 8, ρ_{calcd} = 1.356 g cm⁻³, $\mu(MoK\alpha)$ = 0.0082 cm⁻¹, $F(000)$ = 912, 11890 reflections measured, 5441 are independent (R_{int} = 0.0299) which were used in all calculations, 613 refined parameters and 1 restraints, $R1$ = 0.0628, $wR2$ = 0.1106 (all data). Structure solution and refinement were performed by using SHELXTL via APEX2 software package. Characterization of **6**: $[MH]^+$ = 219 g mol⁻¹; UV-Vis ($CHCl_3$): 255 nm (4.4×10^5), 300 nm (1.3×10^5), 352 nm (2130), 370 nm (1670) and 386 nm (sh). UV kinetic measurement of the deep blue solution shows absorbance at 250 nm, 290 nm, 305 nm (sh), which are all shifted to high energy. At the same time, two obvious absorption peaks at 565 nm and

610 nm appear. CCDC 289915. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b517117b

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