

A new C–C bond forming annulation reaction leading to pH switchable heterocycles†

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A C–C bond forming reaction resulting from the α -addition of carbon based nucleophiles to *N*-bromoethyl phenanthridinium leads to the formation of 2,3-dihydro-12*H*-pyrrolo[1,2-*f*]phenanthridine-based derivatives which undergo reversible ring-opening/closing under pH control.

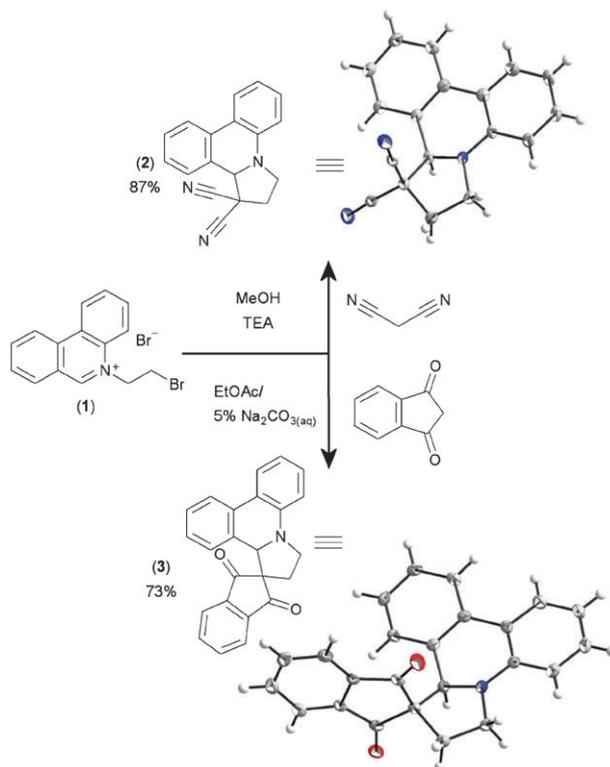
The development of molecular systems capable of switching state, both reversibly and irreversibly, is of interest since they conceptually provide a route for the development of molecular scale devices.¹ Such devices are interesting since switching on the single molecule or cluster level² leads to the possibility of molecular scale information processing, sensing, and switchable catalysis.^{3,4} Devices that have been constructed to date include: molecular shuttles,⁵ switches,⁶ sensors,⁷ valves,⁸ motors⁹ and wires,¹⁰ for which there are numerous successful examples.¹¹ Most examples of molecular switches typically consist of two stable states distinguishable by physical or chemical properties (response), which are interchangeable through the alteration of controllable parameters (stimuli) such as pH, temperature, light, redox potential, and metal ion type/concentration.¹²

A potentially fruitful area for the design of such switchable molecular systems is in the field of heterocyclic chemistry where a great deal of research is concerned with the discovery of new methods of ring formation. If these annulation reactions can be made to act reversibly with respect to an external stimuli they can form the basis of a molecular switching system.¹³ Recent work by us has led to the development of a number of new heterocyclic synthetic methodologies based on the reactivity of *N*-functionalised phenanthridinium derivatives.¹⁴ One such methodology involves the reaction of a primary amine with *N*-bromoethyl phenanthridinium bromide (BEP, **1**), with the primary amine undertaking an α -addition to the phenanthridinium moiety followed by an intramolecular cyclisation reaction and an oxidation step to form a class of dihydro-imidazo-phenanthridinium (DIP) cations. These structures have been shown to exhibit tuneable anti-cancer activity.¹⁵ Further, with the DIP-based systems it is possible to control the formation of the 5 membered ring and the subsequent redox reaction resulting in formal hydride

loss, so the compound is oxidised to form the heterocyclic cation.¹⁶

In this communication we report the discovery of a new C–C bond forming annulation reaction, related to the DIP and aldol addition reactions, which form 2,3-dihydro-12*H*-pyrrolo[1,2-*f*]phenanthridine (DPP) derivatives which can undergo a reversible ring-opening, ring-closing process under pH control. This process can be followed spectroscopically using NMR or UV/vis, and shows how this reaction can be used to form bistable molecular systems.

The reaction utilises carbon based nucleophiles which are familiar as starting material for Knoevenagel and related reactions such as malononitrile and 1,3-indandione as the initial nucleophiles. These starting materials were reacted with BEP (**1**) to yield the cyclised products 2,3-dihydro-12*H*-pyrrolo[1,2-*f*]phenanthridine-1,1-dicarbonitrile (DPP-dicarbo nitrile, **2**)

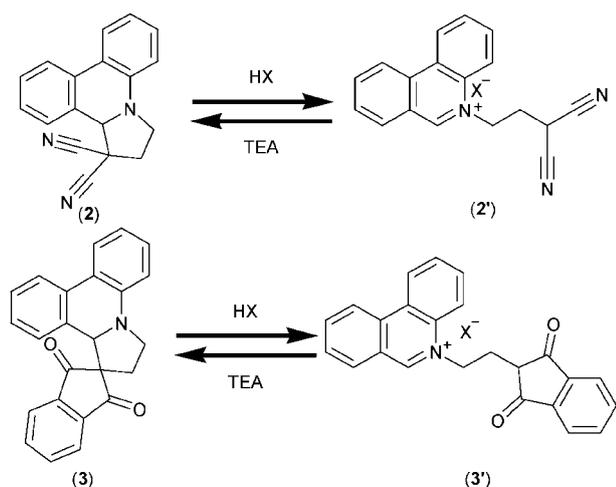


Scheme 1 (left) Reaction of malononitrile and 1,3-indandione with BEP (**1**) to form the cyclised DPP products (**2**) and (**3**). (right) Thermal ellipsoid plots at the 50% probability level of the crystal structures of (**2**) and (**3**).

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Scheme 2 pH controlled reversible cyclisation process of compounds (2) and (3).

and the hexacyclic *spiro*-2,3-dihydro-12*H*-pyrrolo[1,2-*f*]-phenanthridine-1-indandione (DPP-indandione, **3**) in good yield (see Scheme 1). X-Ray crystal structural analysis revealed the structure of these two products which were obtained from crystals formed by slow evaporation of saturated methanolic solutions of the pure materials (see ESI†).

By analogy with the reaction mechanism for the standard DIP reaction reported previously,³ the following mechanism can be proposed for the synthesis of (2) and (3); initial addition takes place at the phenanthridinium α -carbon followed by an intramolecular 5-*exo*-tet cyclisation to form the five membered ring of the product. In contrast to the DIP reaction this product does not then oxidise in the presence of BEP to form the rearomatised cationic species analogous to the DIP structure. Attempts to oxidise (2) and (3) using a variety of oxidising agents were not successful. This resistance to oxidation relative to the DIP structure is most likely due to a lack of possible delocalisation of the positive charge in the oxidised structure which stabilises the DIP cation. DPP heterocyclic

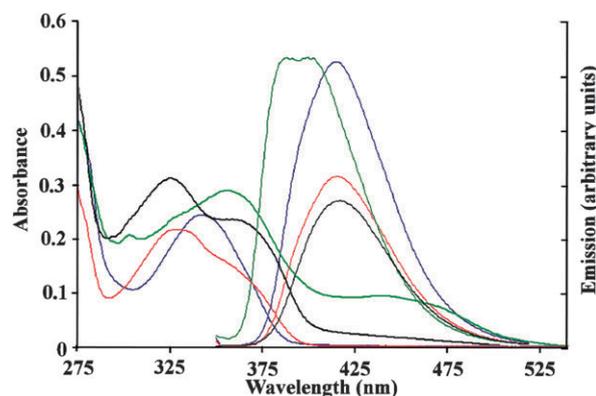


Fig. 2 Absorbance (left) and emission (right) spectra of 5×10^{-5} M solutions of DPP derivatives (**2**, blue) and (**3**, green) and PP derivatives (**2'**, red) and (**3'**, black).

frameworks have previously only been synthetically available by 1,3-dipolar cycloaddition reactions on suitably functionalised phenanthridine starting materials.¹⁷

Treatment of the DPP products (2) and (3) with acid leads to the protonation of the electron deficient carbon atom originating from the malononitrile or 1,3-indandione and rearomatisation of the phenanthridinium ring system forming a ring opened form of the DPP structure, open chain 5-propyl phenanthridinium (PP) derivatives (2') and (3') (see Scheme 2). This ring-opening process has been shown by NMR spectroscopy experiments (see Fig. 1) to be a reversible process whereby addition of TEA to the ring opened form of the molecules facilitates the deprotonation of the carbon followed by an intramolecular 5-*endo*-*trig* cyclisation to regenerate the initial DPP structure (see Scheme 2).

As can be seen from the structures of the ring opened and ring closed forms of the two DPP molecules, these substances will be expected to exhibit differing optical properties due to the differences in the size of the conjugated chromophore in the phenanthridine portion of the structure depending upon the aromaticity of the system. In the original DPP structure

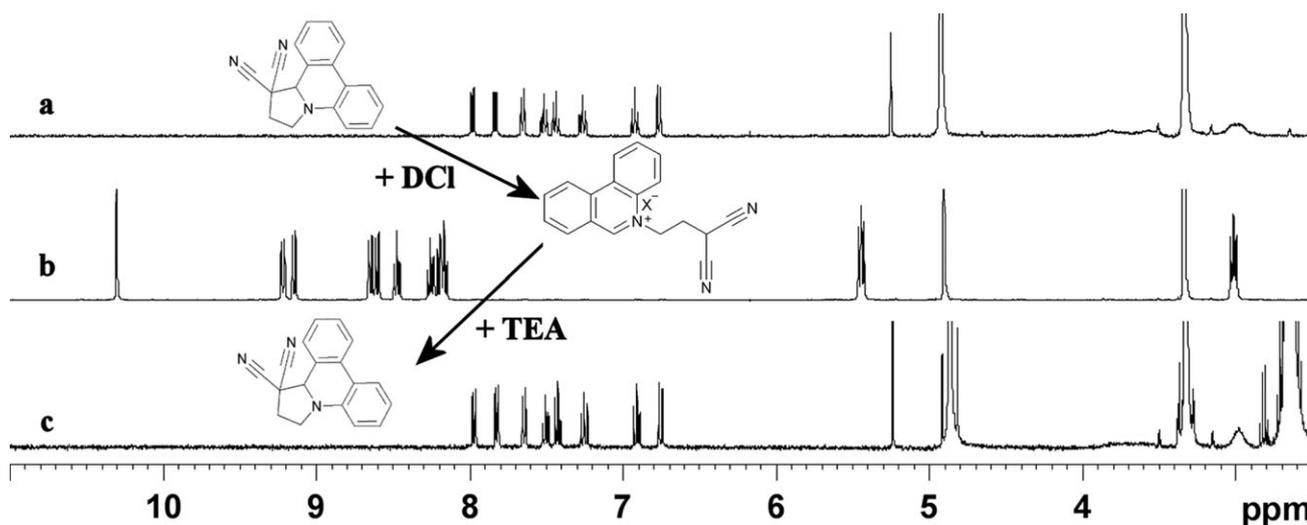


Fig. 1 (a) ¹H-NMR in MeOD of (2), (b) after addition of 1 drop conc. DCl indicating the ring opened form (2') and (c) recycled product after addition of 2 drops TEA. For full assignment of signals, see ESI†.

the aromaticity of the phenanthridine region is interrupted by the central, non-aromatic ring, however in the open chain, PP, form of the molecule the aromatic conjugation extends over the entire phenanthridinium region of the structure.

The two distinct states of this system can be distinguished not only by $^1\text{H-NMR}$ spectroscopy of the material, but also by the significant changes in the chromophore structure of the DPP on conversion to the PP form which leads to a difference both in the UV spectra and fluorescence behaviour of these materials as well. In both of the tested cases the conversion to the PP form of the molecule leads to a shifting of the maximum absorbance in the UV region to a shorter wavelength, from 343 nm for (2) to 327 nm for (2') and from 356 nm for (3) to 326 nm for (3') (see Fig. 2). These changes are most noticeable in the colour of the (3)–(3') system where the DPP (5) form exists as a bright orange powder, while the PP (7) form is bright yellow in colour. The (2)–(2') system also exhibits significant differences in optical properties with UV irradiation of a solution of (2) in methanol producing a visible fluorescence emission, which does not appear once the system has been switched to the ring opened form (2').

In conclusion a new C–C bond forming annulation reaction has been discovered which is related to the aldol reaction and leads to a class of 2,3-dihydro-12*H*-pyrrolo[1,2-*f*]phenanthridine (DPP) derivatives which exhibit a reversible, pH controlled ring-opening–cyclisation process. DPP-type compounds therefore represent a promising lead to produce a family of pH switchable systems in which the properties could be tuned by the choice of substituents on the five membered ring of the DPP structure or on the nucleophile itself.

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