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Cascade Reactions

Phase-Transfer-Catalysed Synthesis of Pyrroloindolines and Pyridoindolines by a Hydrogen-Bond-Assisted Isocyanide Cyclization Cascade

Peter C. Knipe, Matija Gredičak, Artiom Cernijenko, Robert S. Paton,* and Martin D. Smith*[a]

Abstract: A cascade reaction that generates pyrrolo- and pyridoindoline motifs from isocyanide precursors under phase-transfer conditions is described. This transformation proceeds at room temperature in the presence of a quaternary ammonium catalyst and base to generate functionalized products containing an all-carbon quaternary stereocentre. Quantum chemical calculations demonstrated that intramolecular general acid catalysis plays a key accelerating role through stabilization of developing charge in the transition state, and that the reaction is best described as a 5-endo dig cyclization, rather than an anionic 6π electrocyclization. Investigations employing chiral phase-transfer catalysts have given promising selectivities to date.

Pyrrolo- and pyridoindoline motifs are core components of a number of structurally complex natural product families possessing potent biological properties.[1,2] For example, (−)-physostigmine, one of the simplest naturally occurring pyrroloindolines, is a clinically approved acetylcholinesterase inhibitor employed in the treatment of glaucoma, myasthenia gravis and Alzheimer's disease,[3] whereas (−)-communesin A exhibits potent cytotoxicity towards P-388 murine lymphocytic leukaemia cells (Figure 1).[4] The polypyrroloindoline family of alkaloids, of which (−)-hodgkinsine B is an exemplar, have been shown to possess antibacterial, antifungal, antiviral and analgesic properties (Figure 1).[5] Consequently, the synthesis of these structural motifs and the natural products that contain them has been the subject of much elegant and effective research.[6–9] The majority of pyrroloindoline syntheses rely on two strategic disconnections: electrophilic attack at C-3 of an appropriately substituted tryptamine derivative, followed by intramolecular trapping of the resulting iminium ion; and alkylation of oxindoles with subsequent manipulation.[7] Although these methods are extremely robust, as was demonstrated by their use in numerous total syntheses, there are some limitations to their scope. Both routes require electrophilic reagents for the introduction of substitution at the indole C-3 position, and employ substrates generally derived from tryptamine, tryptophan or oxindole, leading to limited substitution patterns in the pyrroloindolines obtained.

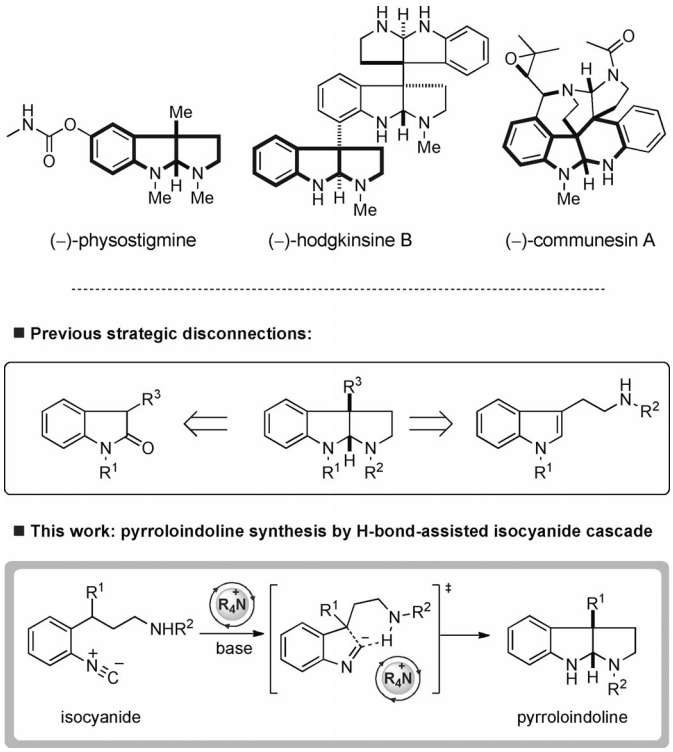

Figure 1. Representative pyrrolo- and pyridoindolines, common strategic disconnections and strategy for isocyanide cyclization cascade.

As part of our on-going studies into the synthesis of substituted and polycyclic indolines,[10] isocyanides were identified as a versatile functional group with the potential to act as a focal point in the synthesis of pyrrolo- and pyridoindolines (Figure 1).*ortho*-Isocyanophenylacetonitriles have been demonstrated to undergo enantioselective 5-*endo-dig* cyclization to afford the corresponding indolenines under basic phase-transfer-catalysed conditions,[11] and we envisaged extending this methodology by introducing an intramolecular nucleophile to trap the resulting indolenine,[12] leading to the formation of pyrrolo- or pyridoindolines in a single operation. Nucleophilic additions to isocyanide groups generally require activation with a Brønsted or Lewis acid or an electrophile, and hence we

[a] Dr. P. C. Knipe, Dr. M. Gredičak, A. Cernijenko, Dr. R. S. Paton, Dr. M. D. Smith
Chemistry Research Laboratory, University of Oxford
12 Mansfield Road, Oxford, OX1 3TA (UK)
E-mail: robert.paton@chem.ox.ac.uk
martin.smith@chem.ox.ac.uk

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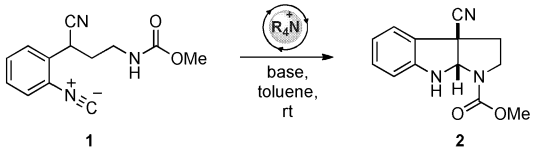
reasoned that a cyclization cascade could be mediated through an intramolecular hydrogen bond from a pendant amide or carbamate.[13] Such a process would constitute a new strategic approach to these privileged structural motifs, providing a new disconnection for total synthesis and the preparation of medicinally relevant structural analogues.

Isocyanide **1** (prepared in five steps from 2-nitrophenylacetonitrile)[14] was subjected to a variety of basic phase-transfer-catalysed conditions to determine the viability of the reaction (Table 1). Of the four quaternary ammonium salts investigated, tetra-*n*-butylammonium chloride (TBAC) was the most effective

Table 1. Optimization of phase-transfer-catalysed synthesis of pyrroloindolines.



1 **2**

Entry	Catalyst[a]	Base	*t*	Yield [%][b]
1	$Bu_4N^+HSO_4^-$	50% KOH (aq.)	30 min	64
2	$Me_3(C_{16}H_{33})N^+Br^-$	50% KOH (aq.)	30 min	40
3	**$Bu_4N^+Cl^-$**	**50% KOH (aq.)**	**30 min**	**76**
4	$Et_4N^+I^-$	50% KOH (aq.)	30 min	72
5	$Bu_4N^+Cl^-$	KOH (s)	30 min	63
6	$Bu_4N^+Cl^-$	K_2CO_3 (s)	72 h	44
7	$Bu_4N^+Cl^-$	50% NaOH (aq.)	30 min	75
8	–	50% KOH (aq.)	168 h	38
9	$Bu_4N^+Cl^-$ (5 mol%)	50% KOH (aq.)	4 h	74
10	$Bu_4N^+Cl^-$ (2 mol%)	50% KOH (aq.)	48 h	62

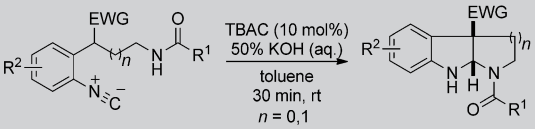
[a] Unless otherwise indicated, catalyst loading was 10 mol%. [b] Isolated yield.

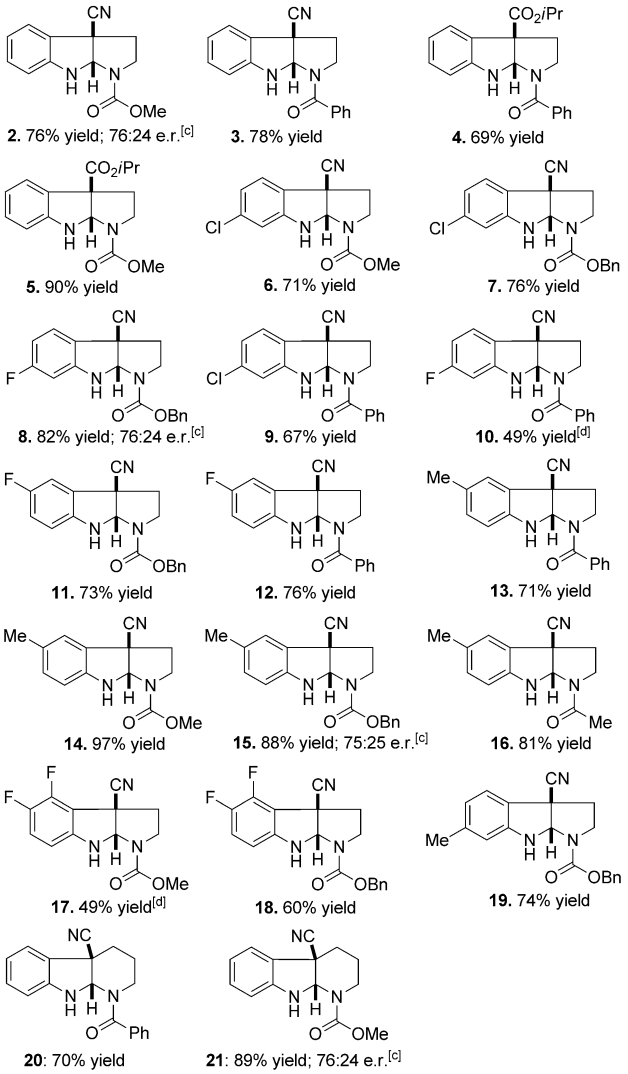
when 50% aqueous potassium hydroxide was employed (Table 1, entry 3), giving the product in 76% yield after 30 min. The use of other bases or of powdered solid potassium hydroxide led to diminished yields, and removal of the phase-transfer-catalyst entirely slowed the reaction significantly, leading to low conversions, even after extended reaction times (Table 1, entries 5–8). Lowering the catalyst loading also increased reaction times and decreased yields (Table 1, entries 9–10). Therefore, the optimized procedure employed 10 mol% TBAC and 50% aqueous potassium hydroxide in toluene, giving the desired pyrroloindoline **2** in 76% yield after 30 min at room temperature.

With optimized reaction conditions in hand, we turned our attention to investigate substrate scope and reaction limitations (Table 2). The transformation maintained its effectiveness upon changing the methyl carbamate group **2** to a benzamide **3** and was tolerant of both benzylic nitriles and esters (**4** and **5**). Introduction of different substituents on the aromatic ring in the preparation of substrates **6**–**19** required slight changes in the synthetic route.[14] Electron-withdrawing and -donating substituents both in *para*- and *meta*- positions (with respect to the aliphatic chain) had little or no influence on product yield or reaction course. The pyrroloindoline synthesis was also successful when *ortho* and *meta*-disubstituted isocyanides were employed (**17** and **18**), and both benzyl carbamate and acetamide groups gave good reactivity (e.g., **19** and **16**). Products were generated exclusively as the *cis*-fused diastereoisomer, in agreement with X-ray crystallographic analysis of **17** and consistent with the much higher ring strain in the *trans*-isomer.[15]

In addition to the pyrroloindolines, pyridoindolines **20** and **21** were formed in high yields, demonstrating a tolerance of both carbamate and amide substituents. Similar to the pyrroloindolines, X-ray crystallographic analysis (of **20**) confirmed that products were generated as a *cis*-fused diastereoisomer.[15]

Table 2. Substrate scope.





[a] Reactions were carried out on 0.1–0.2 mmol scale. [b] Isolated yields; when applicable, these refer to the racemic reaction. [c] Asymmetric reaction carried out on a 10 mg scale; yields were not determined. [d] Calculated from aniline precursor.[17]

Preliminary investigations into asymmetric phase-transfer catalysis of this reaction have yielded promising enantiomeric ratios of up to 76:24 (e.r.), in which *cinchona*-derived catalyst *N*-(2,3,4-trifluorobenzyl)cinchoninium bromide was employed (Table 2, compounds **2**, **8**, **15** and **21**).[16]

Based on the premise that the pendant amide or carbamate proton is a key activating component of the reaction, we propose a plausible mechanism for these transformations (Figure 2). We reasoned that deprotonation at the benzylic position of **22** (necessarily acidified by the adjacent nitrile) would lead to stabilized cyanocarbanion species **23**, which could undergo 5-*endo*-*dig* cyclization as a consequence of an intramolecular hydrogen bond to the isocyanide, to give a transient sp^2 anion **25**.[18] This anion could be quenched in an intramolecular proton transfer, and the resulting *aza*-anion **26** could attack the intermediate indolenine, generating the observed pyrrolo- and pyridoindolines **27** after re-protonation. To investigate the importance of the hydrogen-bond activation of the isocyanide provided by the N–H, we prepared isocyanide *N*-methyl derivative **28** (which cannot function as a Brønsted acid); after 24 h under the optimized cyclization conditions, this substrate failed to generate the corresponding indolenine **29**, with primarily starting material recovered.[19] Cyclization of ^{2}H-labelled **30** under phase-transfer conditions led to **31**, with 17% ^{2}H incorporation observed (average of four experiments). We attribute this to partial ^{2}H/^{1}H exchange (of the N–^{2}H) under aqueous conditions, followed by cyclization by the mechanism depicted.[20]

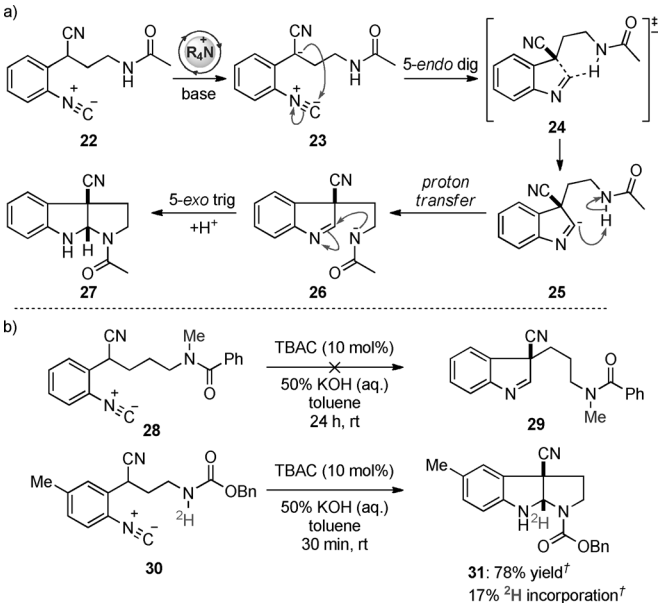


Figure 2. a) Mechanistic proposal for synthesis of pyrrolo- and pyridoindolines; b) experimental investigations into the role of the Brønsted acidic N–H proton. †Values are an average over four runs.

To probe the effect of the putative intramolecular hydrogen bond on cyclization, the reaction free-energy profile of **22** was studied. The carbocyclization step of **22** may occur through a pathway, in which the amide N–H proton is coordinated to the isocyanide, or in which the amide is rotated away and this interaction is entirely absent: both possibilities were modelled, locating a transition structure (TS) in each case (**24** and **32**, respectively). Unequivocally, this N–H···C interaction, with an H–C separation of 2.21 Å, was computed to provide stability in the TS (by 6.5 kcal mol^{-1}) leading to a kinetic acceleration of ring closure. The origin of this kinetic effect is tied with product stabilization by the Hammond postulate (Figure 3).

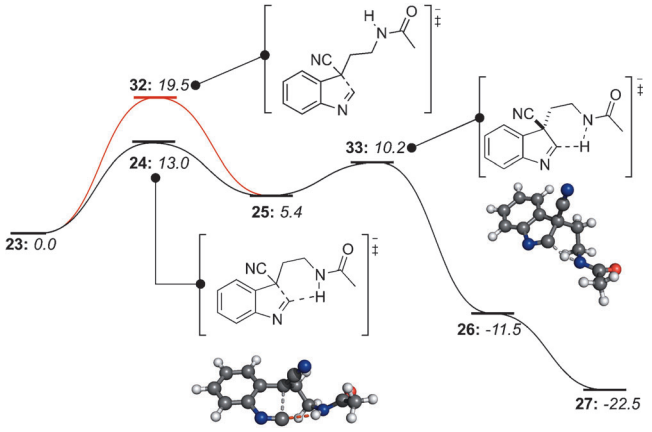


Figure 3. Reaction free-energy profile for hydrogen-bonded and non-hydrogen-bonded cyclization manifolds. Energies (in italics) are quoted in kcal mol^{-1} (B2GP-PLYP/6-311++G(d,p)//CPCM-wB97XD/6-311++G(d,p) G_{rel} at 298 K). Transition structures **24** and **33** are depicted.

The strength of the stabilizing N–H···C hydrogen bond in **24** was determined to be 10.6 kcal mol^{-1},[22] a value comparable in magnitude to N–H···O hydrogen-bonding interactions found in biological systems.[23] Therefore, the rapid carbocyclization observed is a direct consequence of intramolecular hydrogen-bonding catalysis; as a result, the reaction rate would be expected to increase in the presence of a kinetically more labile proton donor. Indolenine carbanion **25** lies uphill (i.e., endergonic) from **23** by 5.4 kcal mol^{-1}, with subsequent exergonic irreversible N to C proton transfer occurring readily via a TS (**33**) only 4.8 kcal mol^{-1} above this intermediate to afford *aza*-anion **26**. The relative ease computed for this second step corroborated the experimental observation of significant deuterium incorporation at this position when an N–^{2}H-labelled substrate was used. Closure of the second ring to form the *cis*-fused bicycle **27** was computed to occur without an energetic barrier.

The key carbocyclization step may be classified as an anionic 5-*endo*-*dig* ring closure, but we were intrigued to establish whether this reaction exhibits the characteristics of a pericyclic (or pseudopericyclic) 6π electrocyclization.[24] The nuclear independent chemical shift NICS(0) values were calculated at the centre of the forming five-membered ring and of the fused aromatic ring along the intrinsic reaction coordinate (IRC).[25] Rather than using isotropic values, which are contaminated by magnetic effects not related to aromaticity,[26] we focused on the out-of-plane *zz* tensor component (Figure 4). For the cyclization of isocyanide **22** the NICS(0)$_{zz}$ tensor of the forming five-membered ring increases from −8.2 to 0.0 ppm along the

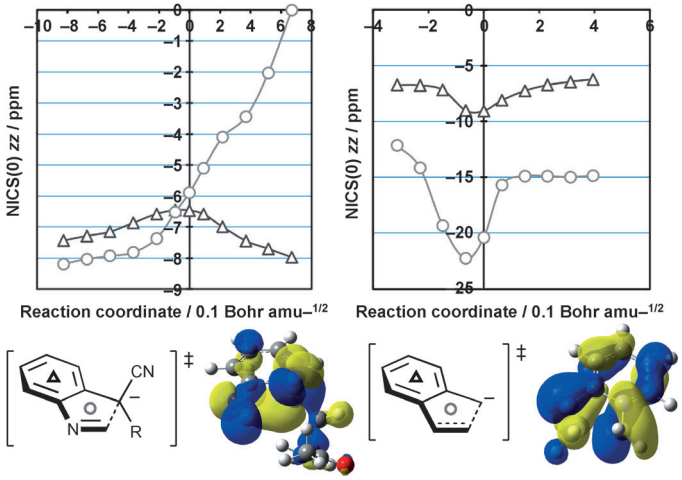


Figure 4. GIAO-B3LYP/6-311++G(d,p)//wB97XD/6-311++G(d,p) NICS(0)$_{zz}$ values for the ring closure in TS **24** and a reference electrocyclization. B3LYP/STO-3G HOMOs in each TS shown below.

IRC. In marked contrast, the same shielding tensor for the all-carbon cyclization decreases from −12.2 to −20.4 ppm in the TS, rising again to −15.0 ppm when the ring is formed. For reference, the NICS(0)$_{zz}$ value of benzene is −14.5 ppm at the same level of theory. On this evidence, TS **24** does not display the characteristic aromaticity of an electrocyclic ring closure. This verdict was further supported by inspection of the HOMO; in compound **24**, this orbital is formed from the delocalized nitrile α-anion attacking the in-plane CN π*, whereas in the reference electrocyclic TS the HOMO is delocalized over both rings. Quantum chemical analysis has also ruled out the involvement of "in-plane aromaticity", as was described by Alabugin,[27] and of a pseudopericyclic orbital interaction as defined by Lemal and expounded by Birney and others.[28–30] Therefore, it is most appropriate to describe the cyclization as an intramolecular hydrogen-bond-catalysed anionic 5-*endo* dig reaction.

A new cascade approach to the synthesis of pyrrolo- and pyridoindolines has been developed, employing isocyanides as a key focal point for the construction of the core bicyclic framework under phase-transfer catalysis. Preliminary investigations demonstrated that *cinchona*-derived ammonium salts can direct the topicity of the reaction with promising levels of enantioselectivity. Intramolecular hydrogen bonding was demonstrated to have a profound stabilizing effect on the transition state of the cyclization, indicating that chiral hydrogen-bond donors may serve as viable asymmetric catalysts for the deployment of isocyanides in complexity-generating reactions. We anticipate that the utility of isocyanides as a central component in the construction of complex heterocycles under both phase-transfer and hydrogen-bonding catalysis will be further explored.

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Keywords: density functional calculations · cascade reactions · heterocycles · hydrogen bonds · isocyanides · phase-transfer catalysis

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