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Novel spiro and fused heterocycles from the allylation of indigo

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ABSTRACT

The allylation of indigo results in the one-step synthesis of two unique complex heterocyclic systems: a spiroindoline–pyridoindolone arising from the addition of three allyl moieties and a fused pyridoindolo-azepinoindolone generated from the addition and subsequent cyclisation of two allyl moieties. The structures of these novel heterocycles are assigned unambiguously using extensive NMR experiments and by X-ray crystallographic analysis. The distribution of the products is influenced by the use of thermal versus microwave heating.

Despite the venerable lineage of indigo and the extensive knowledge of its chemical properties,[1] N- and N,N′-alkylation and subsequent reactions of this compound are not well developed. This can be explained partly by the limited solubility of indigo itself, and also partly by early reports that indigo could not be alkylated[2] or formed complex mixtures[3] on such reactions. This last perception was altered, however, by the later report[4] of a near quantitative formation of *N*,*N*′-dimethylindigo on reaction of indigo in DMF (with a trace of water) with iodomethane in the presence of barium oxide as a base. Other *cis*-*N*,*N*′-bridged indigo derivatives, for example, the 1,2-ethano,[5] 1,3-propano[5,6] and 1,4-butano systems,[5] together with a mono *N*-benzyl derivative,[7,8] can also be accessed by base-induced (NaH) N-alkylation reactions. Added impetus for further investigation arose from the relatively recent discovery of the chlorinated indigo-*N*-glycosides, Akashin A, B and C from a *Streptomyces* sp.;[9] these compounds have significant anti-tumour activity against a range of human tumour cell lines.[10]

As part of a continuing programme investigating functionalised biaryls as molecules with potential bioactivities and subsequent therapeutic uses,[11] we became interested in the N-substitution reactions of the readily available dye, indigo, with its embedded 2,2′-bis-indolic system. In this context we investigated the allylation of indigo, as this was expected to provide derivatives with better solubility profiles as well as to introduce useful functionality for subsequent reactions, for example, metathesis reactions. The allylations resulted in the serendipitous and unprecedented one-pot formation of two unusual heterocyclic systems and the results are reported in this Letter.

Initially, a suspension of indigo **1** and caesium carbonate in anhydrous DMF at 70 °C was treated with allyl bromide (5 mol equiv). After filtration and silica gel chromatographic separations, the *N*-allylisatin **2**[12] was isolated in 25% yield along with the 1-allyl-5′-allyloxy-3′,4′-dihydrospiroindoline-pyrido[1,2-*a*]indol-one **3** (32% yield) and the pyridoindolo-azepino[1,2-*a*]indol-11(7*H*)-one **4** (11% yield). Indigo was recovered (23%) giving an overall atom return of 91% (Table 1, entry 1).[13]

Initial sonication of **1** in DMF ensuring maximal dissolution was required for optimal yields. Our subsequent attempts at reaction optimisation involved the use of a microwave reactor[14] under sealed reaction conditions. Surprisingly, this resulted in the seven-membered structure **4** being the major product and the spiro heterocycle **3** being the minor product (Table 1, entry 2). This inversion of major product to minor product was also observed for entries 3 and 4. Further extensions of the reaction involved the use of different allyl substituents, and the results are summarised in Table 1. In all cases, the spiro structure **B** was formed with the exception of the *gem*-dimethyl allyl examples (entries 9 and 10), where presumably steric interactions prevented the cyclisation to either structure. Here, only

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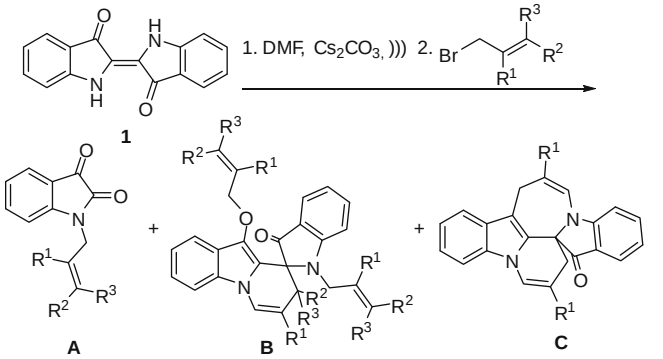
Table 1
The allylation of indigo to produce allylisatins (**A**), spiroindoline–pyridoindolones (**B**), and pyridoindolo-azepinoindolones (**C**)



Entry	R^1	R^2	R^3	Δ	**1** %		**A** %		**B** %		**C** %
1	H	H	H	Thermal	23	**2**	25	**3**	32	**4**	11
2	H	H	H	μwave	16	**2**	14	**3**	11	**4**	38
3	Me	H	H	Thermal	18	**5**	22	**6**	36	**7**	9
4	Me	H	H	μwave	15	**5**	12	**6**	10	**7**	35
5	H	Me	H	Thermal	6	**8**	14	**9**	42		
6	H	Me	H	μwave	17	**8**	6	**9**	12		
7	H	Ph	H	Thermal	21		—[a]	**10**	12[b]		
8	H	Ph	H	μwave	15		—[a]	**10**	9[b]		
9	H	Me	Me	Thermal	63	**11**	14				
10	H	Me	Me	μwave	58	**11**	3				

[a] (—) indicates that this product was not isolated from the reaction.
[b] Approximately 5% of an isomer probably arising from olefin migration is present as indicated by ^{1}H NMR analysis.

the allylisatin **11** and unreacted indigo were isolated. In the cases of mono-terminal substitution of the allyl derivatives (entries 5–8), steric hindrance also appears to be playing a role, with the formation of the corresponding spirocyclic structures **9** and **10** but with no evidence of the fused heterocycles.

The structure of **3** was initially determined using an array of NMR experiments. Foremost was the differentiation between the possible positions of the double bond within the pyrido ring. Confirmation of the presence of the enamine arose from the observation of key correlations including the diastereotopic protons $H2'_A$ and $H2'_B$ coupling to the spiro carbon as indicated by analysis of the gHMBC spectrum; the latter carbon was assigned as quaternary from the DEPT spectrum analysis. Final structural confirmation of the products came from X-ray crystallographic analysis of *N*-allylisatin **2**, the spiroindolone **9** and the azepino-indolone **4** (Fig. 1).

For the spiro derivative **9**, with two stereogenic atoms at positions 2′ and 2, potential for diastereomers existed. However, in the ^{13}C NMR spectrum of **9** no doubling of peaks was apparent and therefore it is likely that only one pair of enantiomers is present. The crystal structure confirmed the relative stereochemistry with the C2′ proton substituent cis to the indolone *N*-allyl substituent and this disposition was reflected in the observation of an NOE interaction between H2′ and the allyl methylene group. Similarly, with the spiro derivative **10** only one diastereomer was isolated.

Further support for the structure **3**, rather than the alternative adduct where the double bond is in the 2′,3′-position, came from analysis of the calculated minimum energies of each.[16] The conjugated enamine **3** had a minimum energy of 124.086 kcal/mol versus 127.621 kcal/mol for the non-conjugated analog.

The heterocyclic systems embodied in compounds of types **B** and **C** have not been described previously. However, in the case of **B**, the pyrido[1,2-*a*]indolic moiety is well known and derivatives are of considerable pharmacological interest.[17] There are no relatives of system **C**, although a recent paper described a weakly cytotoxic indolic azafulvene marine natural product, pseudocerosine, with partial similarities.[18]

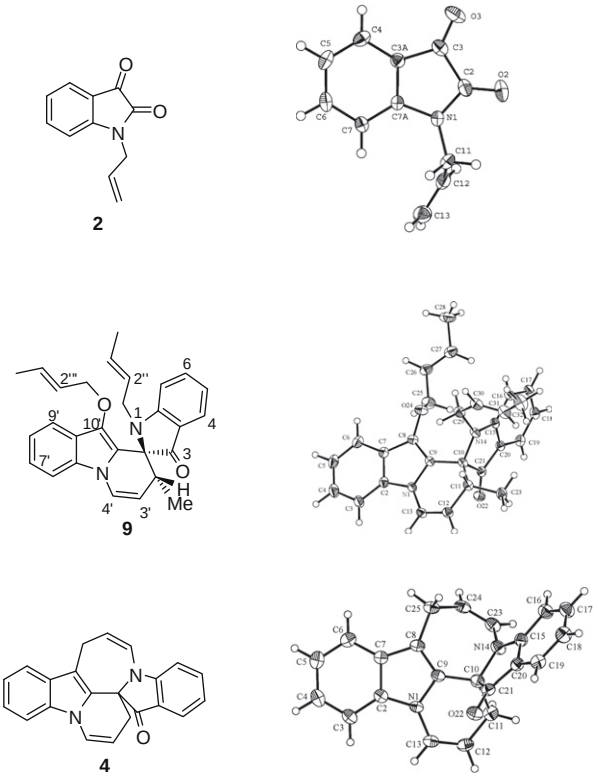
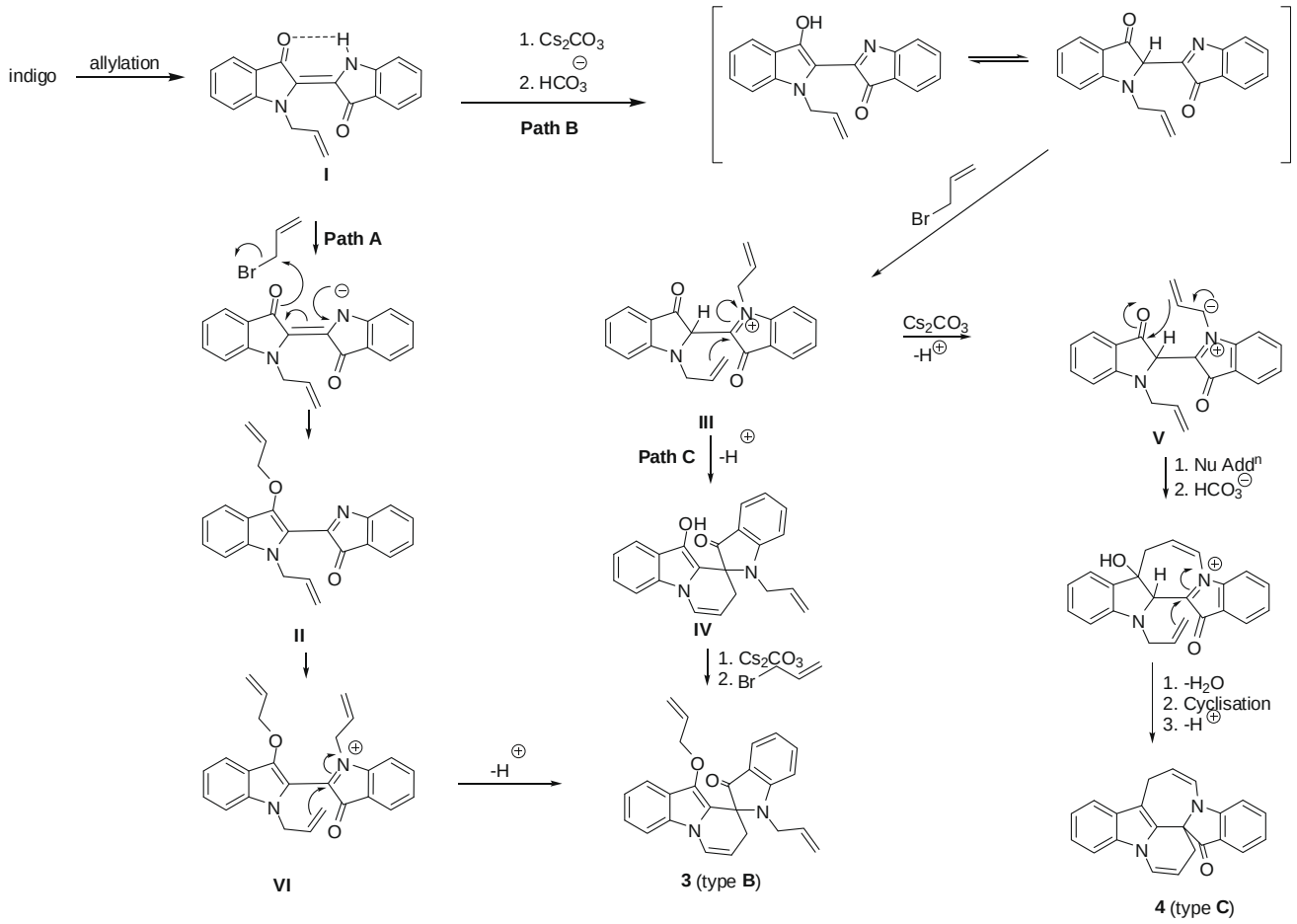


Figure 1. X-ray structures of *N*-allylisatin **2**, spiroindoline–pyridoindol-one **9** and the pyridoindole-azepinoindolone **4**.[15]

A proposed mechanism for the formation of **3** and **4**, as models for compounds of types **B** and **C**, respectively, is outlined in Scheme 1. After the initial formation of the monoallylated indigo intermediate **I** from allylation of the indigo mono anion, deprotonation with subsequent enolisation allows for further *O*-allylation (Path A). A third allylation on the imine nitrogen in **II** might then take place providing a powerful electrophilic site for internal double bond attack and subsequent proton loss to give the spirocyclic derivative **3** of the type **B**. Alternatively, base-induced isomerisation of *N*-allylindigo **I** could take place to give the 3-hydroxyindolic tautomer in equilibrium with its 3-indolone tautomer (Path B). Quaternisation of the imine nitrogen in either tautomer by reaction with allyl bromide could then give the intermediate **III** which is set up for internal nucleophilic attack by the electron-rich alkene on the electron-deficient iminium ion to afford the spiro system **IV** and then **3** (Path C). Alternatively, **III** could form the stabilised allylic zwitterion **V** followed by intramolecular nucleophilic addition on the indolone carbonyl. Subsequent loss of water and final cyclisation would realise the azepino-indolone **4** of the type **C**. The diastereoselectivity observed with the spiro compounds **9** and **10** presumably arises from the necessarily constrained approach of the nucleophilic (*E*)-allylic double bond from both the top and the bottom face in the relevant intermediates of type **III** or **VI**. This would afford the 2′*R*,2*S*:2′*S*,2*R* enantiomeric pair of isomers in the case of **9**, and the 2′*S*,2*S*:2′*R*,2*R* pair for **10**. However, the reasons for the differences in yields with microwave versus thermal heating are not readily apparent at this stage.

Formation of the *N*-allylisatin **2** presumably arises from oxidative cleavage of the *N*-allylindigo intermediate and/or from *N*,*N*′-diallylindigo which could be readily formed from the former under basic conditions with allyl bromide. Oxidative cleavage of *N*,*N*-dialkylindigo derivatives has been reported previously although an oxidant (nitric acid) was used.[3] Oxygen from the air may be an oxidant in the current reactions although when the reaction with



Scheme 1. Proposed mechanistic scheme for the formation of compounds of types **B** and **C**.

allyl bromide was repeated under nitrogen no change in the yield of **2** was seen.

In support of the above-mentioned mechanistic proposals, mass spectrometric evidence for the presence of low yields of *N*-allyl- and *N,N′*-diallylindigo was seen in the crude reaction mixture. Also, reaction of *N*-allylindigo separately with allyl bromide and caesium carbonate in DMF at the lower temperature of 60 °C resulted in the formation of *N,N′*-diallylindigo and compounds **2**, **3** and **4**.

In summary, a new illustration of atom efficiency and domino reaction-based conciseness in heterocyclic synthesis has been revealed through the preparation of two unique, structurally complex and potentially biologically interesting heterocyclic systems from the one-step reaction of the readily available dye, indigo, with allylic bromides in the presence of base. Given the structural complexity of the heterocycles of types **B** and **C**, any attempts at a retrosynthetic analysis would have been unlikely to have proposed indigo as the starting material in such a one-pot process. It is the facile synthetic access to these systems, coupled with their associated functional groups, which provide scope for a range of further transformations including cyclisation reactions to produce more complex, and potentially useful heterocycles. Scope also exists to use other readily available indigo derivatives with different ring substituent groups, for example, indigo carmine, to broaden the product properties, a feature likely to be of importance in future biological activity studies.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.098.

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12. Aboul-Fadi, T.; Abdel-Hamid, F.; Hassan, E. A. *Arch. Pharmacol. Res.* **2003**, *26*, 778–784.
13. Despite the excellent atom recovery, a number of very minor unidentified coloured products were present.
14. Microwave reactor used was a CEM Discover. Individual reaction conditions are reported in the Supplementary data.
15. Structure **2** $C_{11}H_9NO_2$, $M_r = 187.2$. Orthorhombic, $P2_12_12_1$, $a = 6.745(3)$, $b = 9.055(4)$, $c = 14.852(6)$ Å (T ca. 150 K), $Z = 4$. R_1, $wR_2 = 0.036$, 0.101 for 1335 unique ($1269 > 2\sigma(I)$) CCD reflections. CCDC 721339. Structure **4** $C_{22}H_{16}N_2O$. $M_r = 324.4$. Triclinic, $P\bar{1}$, $a = 8.2014(4)$, $b = 13.4942(10)$, $c = 16.5073(9)$ Å, $\alpha = 107.853(3)$, $\beta = 91.354(4)$, $\gamma = 91.958(3)^\circ$ (T ca. 200 K), $Z = 4$. R_1, $wR_2 = 0.045$, 0.121 for 6158 ($3647 > 2\sigma(I)$) CCD reflections. Unresolved lattice solvent was modelled using SQUEEZE. CCDC 723874. Structure **9** $C_{28}H_{28}N_2O_2$. $M_r = 424.5$. Monoclinic, $P2_1/n$, $a = 13.3380(3)$, $b = 12.2113(3)$, $c = 14.9625(4)$ Å, $\beta = 107.903(1)^\circ$ (T ca. 200 K), $Z = 4$. R_1, $wR_2 = 0.046$, 0.134 for 5314 ($3648 > 2\sigma(I)$) CCD reflections. Conformational disorder (0.685(7):0.315(7)) is found in the $CH{:}CHCH_3$ terminus of the OC_4H_7 string. CCDC 723875.
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