ELECTROCYCLIC RING CLOSURE OF 1-AZATRIENES AS A ROUTE TO THE INDOLO[3,2,1-*ij*][1,6]NAPHTHYRIDINE RING SYSTEM [#]

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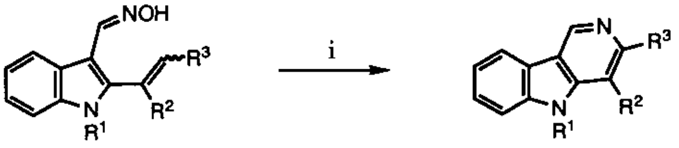
Abstract– Methods of annelation of indole across the 1- and 2-positions have been explored using both the intramolecular Heck reaction and Dieckmann cyclisation. Two examples **5** and **7** of the title ring system have been produced by the thermal cyclisation of indole-3-carboxaldehyde oximes with an alkenyl substituent at C-2.

The electrocyclic ring closure of 1-azatrienes constitutes a useful method for the construction of the pyridine ring system. In particular, oximes, oxime ethers and dimethylhydrazones derived from unsaturated aldehydes have been used recently in several syntheses of fused pyridines.[1] Hibino and co-workers have made extensive use of this reaction as a method of annelation of indoles[2] (Scheme 1).



Scheme 1 . i, toluene, 110 °C.

The aim of the work described in this Communication was to explore the method as a route to polycyclic ring systems with an additional ring fused across the 1- and 2- positions of indole (R^1 and R^2 in Scheme 1). The

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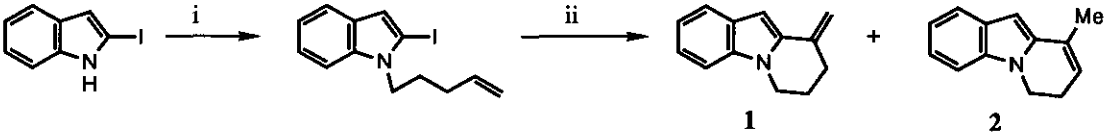
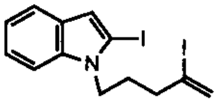
[#] Dedicated to Professor Alan R. Katritzky, FRS, on his 65th birthday.

first target was the indole (**1**). We wished to prepare this compound by making use of the intramolecular Heck reaction as shown in Scheme 2: Grigg and co-workers have made considerable use of this method to produce other types of annelated indole.[3] The starting material was indole; this was converted into 2-iodoindole by a literature procedure[4] which makes use of the excellent methodology introduced by Katritzky[5] for 2-lithiation. *N*-Alkylation with 5-bromo-1-pentene gave the indole suitable for the Heck cyclisation. The Heck reaction proceeded well under mild conditions but it always led to the formation of an inseparable mixture of the required alkenylindole (**1**) and its isomer (**2**). Grigg and co-workers have found that double bond isomerisation can be minimised by using thallium(I) acetate as a co-catalyst.[6] In this reaction we found that the cyclisation was accelerated by thallium acetate but that the double bond isomer (**2**) was always present as a significant minor product.



Scheme 2 . i, Br(CH$_2$)$_3$CH=CH$_2$, NaH (95%);
ii, Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%), TlOAc, MeCN, 80 °C (84%) (**1**:**2** = 3:1)



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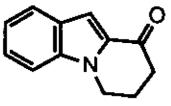

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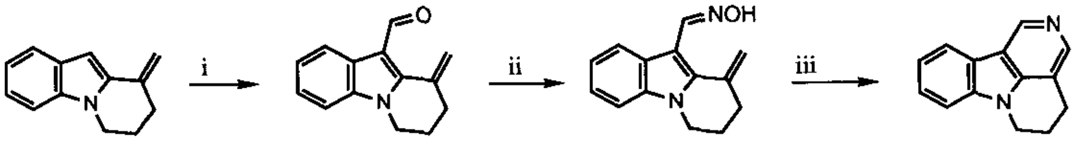
Alternative approaches to compound (**1**) were sought which would minimise the problem of isomerisation. The alkenylindole (**3**) was prepared from 2-iodoindole and 2,5-diiodopent-1-ene[7] and was subjected to palladium catalysed cross coupling. This gave compound (**1**) but in low yield. A bettter approach proved to be a Wittig reaction with the known[8] ketone (**4**) which was prepared, according to the literature procedure, by a Dieckmann cyclisation method starting from ethyl indole-2-carboxylate. Reaction of the ketone (**4**) with triphenyl-phosphonium methylide gave compound (**1**) in good yield.[9]

A standard series of reactions, as outlined in Scheme 3, gave 5,6-dihydro-4*H*-indolo[3,2,1-*ij*][1,6]naphthyridine (**5**).[9] There is only one other report of derivatives of this ring system.[10] As with the examples reported by Hibino and co-workers, the cyclisation took place in toluene. The analogous oxime (**6**) containing a fused five-membered ring, which we prepared in a similar way starting with an intramolecular Heck reaction, failed to cyclise, however. This is presumably due to the extra strain which would be introduced by cyclisation.



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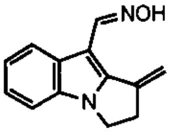
Scheme 3 . i, $POCl_3$, DMF (72%); ii, $HONH_3^+ Cl^-$, KOAc (31%); iii, toluene, 110 °C (65%)



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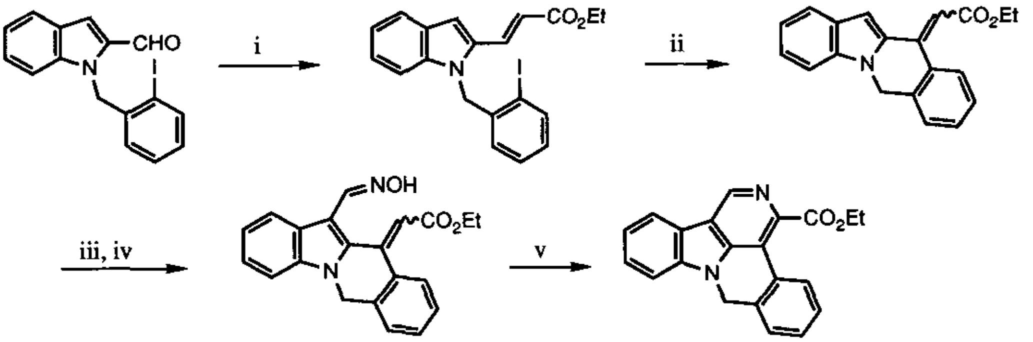
A different type of intramolecular Heck reaction was used to prepare another example of this ring system (7) [9] containing an additional fused benzene ring. This reaction series was explored because the use of the benzyl substituent removes the possibility of double bond isomerisation in the Heck reaction. The series of reactions used to prepare compound (7) is outlined in Scheme 4.



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Scheme 4 . i, $(EtO)_2POCH_2CO_2Et$, KOH (74%); ii, $Pd(OAc)_2$, PPh_3, TlOAc, MeCN, 80 °C (90%); iii, $POCl_3$, DMF (57%); iv, $HONH_3^+ Cl^-$, KOAc (76%); v, toluene, 110 °C (60%)

Indole-2-carboxaldehyde was alkylated with 2-iodobenzyl chloride. A Horner-Emmons reaction was then used to convert the 2-aldehyde into an αβ-unsaturated ester. The Heck reaction led to a mixture of stereoisomers which was carried through the subsequent steps. The electrocyclisation again proceeded in boiling toluene and gave the ester (7) in moderate yield. This indicates that the methods are capable of being extended to allow the preparation of other novel fused indoles.

ACKNOWLEDGEMENT

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9. **1**, mp 82–84 °C; δ (400 MHz, $CDCl_3$) 2.20–2.28 (2 H, m), 2.54–2.57 (2 H, m), 3.99 (2 H, t, *J* 6.0 Hz), 4.96 (1 H), 5.59 (1 H), 6.72 (1 H), 7.05 (1 H, t, *J* 7.4 Hz), 7.11 (1 H, t, *J* 7.4 Hz), 7.15 (1 H, d *J* 8.0 Hz), and 7.54 (1 H, d, *J* 7.8 Hz). **5**, mp (decomp.) 270 °C; δ (400 MHz, $CDCl_3$) 2.29–2.35 (2 H, m), 3.03 (2 H, t, *J* 6.2 Hz), 4.19 (2 H, t, *J* 5.8 Hz), 7.28 (1 H, t, *J* 7.4 Hz), 7.40 (1 H, d, *J* 8.0 Hz), 7.49 (1 H, t, *J* 7.6 Hz), 8.11 (1 H, d, *J* 8.0 Hz), 8.29 (1 H), and 9.12 (1 H). **7**, mp 178–180 °C; δ (400 MHz, $CDCl_3$) 1.38 (3 H, t, *J* 7.2 Hz), 4.47 (2 H, q, *J* 7.2 Hz), 5.33 (2 H), 7.13–7.67 (7 H, m), 7.99 (1 H, d, *J* 7.8 Hz), and 8.93 (1 H).
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