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Indirect N-vinylation of indoles via isomerisation of N-allyl derivatives: synthesis of (±)-debromoarborescidine B

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ABSTRACT

Double bond migration in *N*-allylindoles has been investigated as a method to access *N*-vinyl derivatives of this heterocycle. The optimal reaction conditions employed *t*-BuOK or NaH in DMSO as the solvent at room temperature to afford the products in yields ranging from 51 to 99%. Although in some cases a high degree of stereoselectivity was observed, preferential formation of either the *Z*- or *E*-isomer was not predictable. The developed methodology was employed in the synthesis of (±)-debromoarborescidine B.

Indole alkaloids are a large group of natural products with diverse chemical structures and a wide spectrum of biological properties.[1] As appealing and challenging synthetic targets, they attract significant attention from organic chemists.[2] The indole skeleton is also a structural component of many drugs currently in the market, such as triptans.[3]

As a part of our ongoing research on the synthesis of indole alkaloids possessing an *N*-vinyl moiety, exemplified by natural products **1a**, **2**–**4** (Fig. 1),[4] we searched for a mild, functional group tolerable procedure for the N-vinylation of indoles that would allow further annelation via ring-closing methathesis (RCM). A number of methods describing the introduction of complex *N*-vinyl moieties have been reported in the literature.[5] On the other hand, insertions of unsubstituted or simple *N*-vinyl functionality, suitable for further RCM elaboration, are rare and often require gaseous reactants (acetylene or vinyl bromide), or harsh conditions (KOH, 100 °C).[6] Contrary to a direct N-vinylation, the two step procedure, involving N-allylation followed by double bond migration, to form an *N*-vinyl functionality, is also feasible. The *N*-allyl to *N*-vinyl isomerisation has been investigated extensively.[7] Upon isomerisation, the *N*-vinyl product can be hydrolysed to afford a carbonyl compound and this sequence is vital in the industrial production of menthol.[8] Since the allyl functionality is a useful *N*-protecting group, the isomerisation/hydrolysis sequence is also an integral part of the deprotection strategy of various *N*-allyl derivatives.[9] Additionally, tandem isomerisation–RCM reactions have been utilised successfully in the synthesis of several heterocyclic compounds.[10] The double bond migration in *N*-allyl derivatives can be accomplished with various reagents, from acids and bases to supported metals and transition metal complexes.[7] Metal complexes, in particular, have been investigated extensively leading to a good understanding of these processes and the development of highly stereoselective transformations.[11]

Our initial attempts to promote migration of a double bond in allylindole **5** are outlined in Table 1. The use of several transition metal complexes under mild conditions failed (Scheme 1, Table 1,

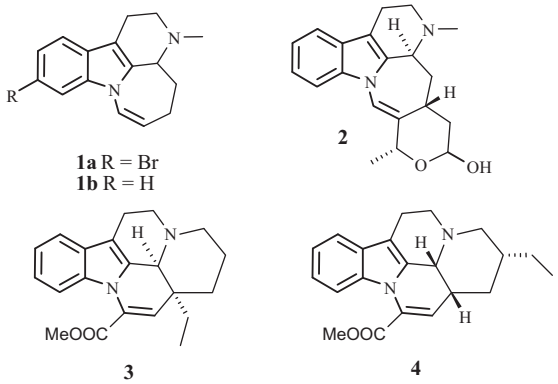

Figure 1.

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Table 1
Reaction conditions for the double bond migration

Entry	Conditions	*Z*/*E*[a]	Yield[b] (%)
a	$Ru(CO)(PPh_3)_3H_2$ (10 mol %), THF, rt	—	—
b	$Rh(PPh_3)_3Cl$ (5 mol %), toluene, rt	—	—
c	allylMgBr (4 equiv), Et_2O, rt	—	—
d	Cs_2CO_3 (4.5 equiv), DMSO, rt	—	—
e	DBU (4.5 equiv), DMSO, rt	—	—
f	*t*-BuOK (0.2 equiv), DMSO, rt	—	—
g	*t*-BuOK (1 equiv), DMSO, rt	—	—
h	*t*-BuOK (2.2 equiv), DMSO, rt	—[c]	33 (50)[d]
i	*t*-BuOK (4.5 equiv), DMSO, rt	*E*[e]	85 (99)[d]
j	*t*-BuOK (4.5 equiv), DMF, rt	*E*[e]	88 (99)[d]

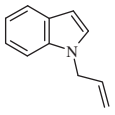
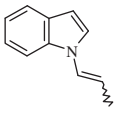
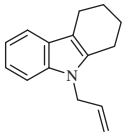
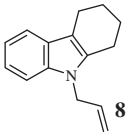
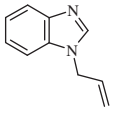
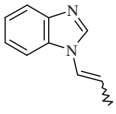
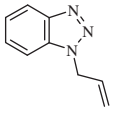
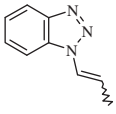
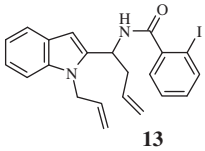
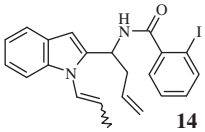
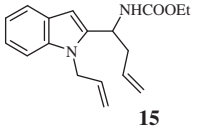
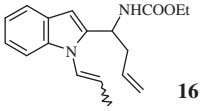
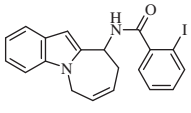
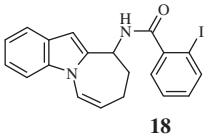
[a] Established by analysis of the ^1H NMR spectra of the crude reaction mixtures.
[b] Isolated yield after column chromatography.
[c] Not determined.
[d] Conversion is given in parentheses.
[e] The ^1H NMR spectrum showed the presence of a trace amount of the *Z* isomer.

Scheme 1.

entries a and b), resulting in recovery of the starting material. Similar results were obtained using a Grignard reagent (Scheme 1, Table 1, entry c). The use of *t*-BuOK in these processes at room temperature and in DMSO as the solvent resulted in the formation of the expected product **6** but, as shown, it was dependent on the amount of the base used. Catalytic or equimolar amounts of *t*-BuOK were not efficient (Scheme 1, Table 1, entries f and g). Increasing the amount of base to 2.2 equiv afforded the product in 33% yield, but with only 50% conversion (Scheme 1, Table 1, entry h). A further increase in quantity of the base resulted in the formation of *N*-vinyl derivative **6** in excellent yield (Scheme 1, Table 1, entry i). Analysis of the ^1H NMR spectral data showed the product to be the *E*-isomer contaminated with only a trace amount of the *Z*-isomer. DMF as the solvent proved to be as efficient as DMSO (Scheme 1, Table 1, entry j). Attempts were also made to use weaker bases, such as Cs_2CO_3 or DBU (Scheme 1, Table 1, entries d and e) at room temperature, but these reactions resulted in recovery of the starting material.

Using the *t*-BuOK/DMSO conditions (Table 2, conditions A),[12] we explored briefly the scope of this transformation and the results are outlined in Table 2. In addition to indole derivatives, benzimidazole **9** and benzotriazole **11** were shown to be suitable substrates (Table 2, entries c and d). Although the reactions produced *N*-vinyl derivatives **10** and **12**, slightly lower yields were observed. Since benzimidazole and benzotriazole are expected to be better leaving

Table 2
Base-promoted *N*-allyl to *N*-vinyl isomerisations

Entry	Starting material	Product	Conditions[a]	Yield[b] *Z*/*E*	Conditions[a]	Yield[b] (%) *Z*/*E*[c]
a	 **5**	 **6**	A	85 (*E* only)	B	73 (4.7:1)
b	 **7**	 **8**	A	99 (1:5)	—	—
c	 **9**	 **10**	A	68 (5:1)	B	64 (9:1)
d	 **11**	 **12**	A	51 (1:8)	B	70 (1:16)
e	 **13**	 **14**	A	95 (2:1)	—	—
f	 **15**	 **16**	A	56 (4:1)	B	60 (Z only)
g	 **17**	 **18**	A	79	—	—

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