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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,

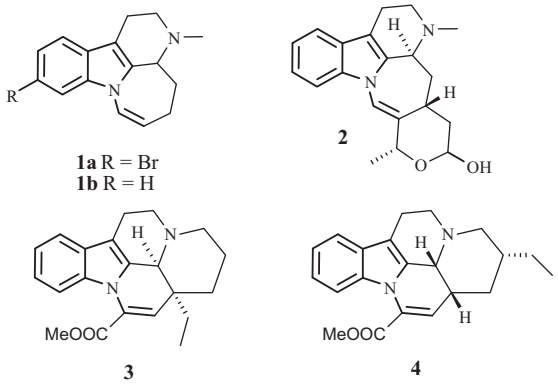

Figure 1.

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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]

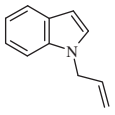
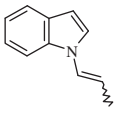
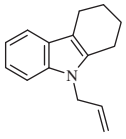
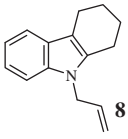
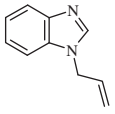
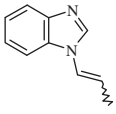
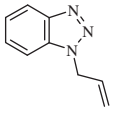
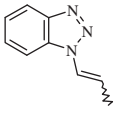
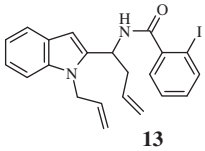
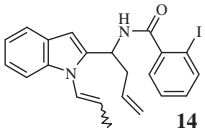
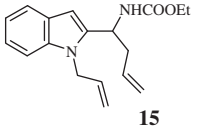
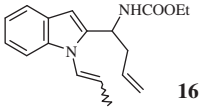
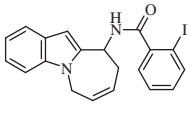
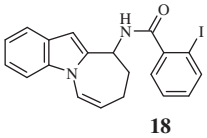
[a] Established by analysis of the ^1H NMR spectra of the crude reaction mixtures.
[b] Isolated yield after column chromatography.
[c] Not determined.
[d] Conversion is given in parentheses.
[e] The ^1H NMR spectrum showed the presence of a trace amount of the *Z* isomer.

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.

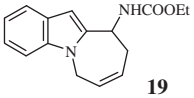
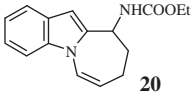
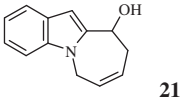
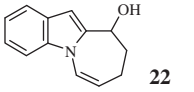
Using the *t*-BuOK/DMSO conditions (Table 2, conditions A),[12] we explored briefly the scope of this transformation and the results are outlined in Table 2. In addition to indole derivatives, benzimidazole **9** and benzotriazole **11** were shown to be suitable substrates (Table 2, entries c and d). 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

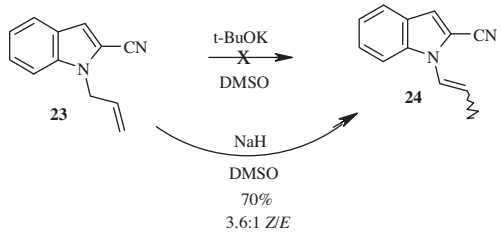
Entry	Starting material	Product	Conditions[a]	Yield[b] *Z*/*E*	Conditions[a]	Yield[b] (%) *Z*/*E*[c]
a	 **5**	 **6**	A	85 (*E* only)	B	73 (4.7:1)
b	 **7**	 **8**	A	99 (1:5)	—	—
c	 **9**	 **10**	A	68 (5:1)	B	64 (9:1)
d	 **11**	 **12**	A	51 (1:8)	B	70 (1:16)
e	 **13**	 **14**	A	95 (2:1)	—	—
f	 **15**	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

(*continued on next page*)

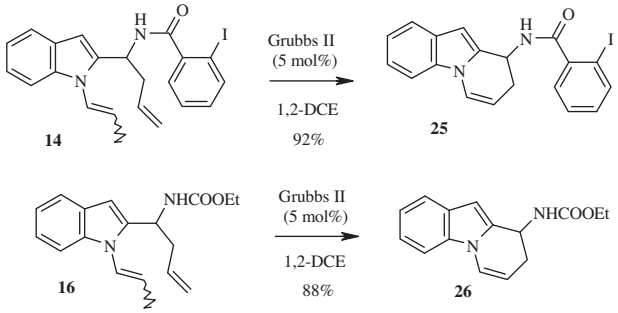
Table 2 (*continued*)

Entry	Starting material	Product	Conditions[a]	Yield[b] *Z*/*E*	Conditions[a]	Yield[b] (%) *Z*/*E*[c]
h	 **19**	 **20**	A	97	B	80
i	 **21**	 **22**	A	98	—	—

[a] Conditions **A**: allyl compound (0.1 mmol), *t*-BuOK (0.45 mmol), DMSO (3 mL), rt, TLC monitoring (reaction times: 1–3 h); conditions **B**: allyl compound (0.1 mmol), NaH (0.45 mmol), DMSO (3 mL), rt, TLC monitoring (reaction times: 3–24 h).
[b] Isolated yield after column chromatography.
[c] Established by analysis of the ^{1}H NMR spectra of the crude reaction mixture.



Scheme 2.



Scheme 3.

groups than indole, they may participate in side processes such as the S_N2 reactions involving the allyl moiety and the nucleophilic base. Generally, simple *N*-allyl heterocycles (Table 2, entries a, b and d) produced a mixture of geometric stereoisomers with the *E*-isomer being the major product. The exception was benzimidazole **9**, which gave completely opposite results (Table 2, entry c). As we intended to use this methodology for the synthesis of some indole-based natural products, the efficiency of the process was tested on more complex substrates (Table 2, entries e–i). Bis-allylated compounds **13** and **15** (Table 2, entries e and f) were isomerised highly chemoselectively and, contrary to most of the above examples, with preference for the *Z*-stereoisomer. The presence of amide, carbamate, aryl iodide or an additional alkene functionality did not interfere with the reaction pathway. Cyclic *N*-allyl derivatives were also suitable substrates for this transformation (Table 2, entries g–i). The isomerised products, **18**, **20** and **22**, were isolated in good yields, and, again, the conditions tolerated the presence of various functional groups.

Attempts to isomerise indole derivative **23** using the above conditions surprisingly failed (Scheme 2). Upon mixing **23** and the base in DMSO the reaction mixture instantaneously turned black, while TLC showed the presence of only a baseline material. As the electron acceptor functionality, the nitrile is likely to facilitate S_N2 processes on the allyl moiety, but also is itself prone to nucleophilic additions. Although *t*-BuOK is often used as a base in synthetic transformations, it possesses nucleophilic properties as well. Bearing in mind that hydride is a weak nucleophile due to its low polarisability, we hoped to suppress the side processes by using NaH. Gratifyingly, replacing *t*-BuOK with NaH resulted in the formation of the expected product **24** in a good yield as 3.6:1 mixture of *Z*- and *E*-isomers. This outcome prompted a brief exploration of NaH in the isomerisation process and the results are summarised in Table 2 (conditions B). In all of the cases investigated (Table 2, entries a, c, d, f and h) the products were isolated in good yields with variable *Z*/*E* selectivity. Compared to the *t*-BuOK method, the process employing NaH as the base seemed to be slightly less efficient requiring generally longer reaction times (1–3 h for *t*-BuOK reactions vs 3–24 h for NaH reactions, as monitored by TLC).

The vinyl indoles prepared by the described methods were shown to participate efficiently in RCM transformations (Scheme 3).

The methodology described above has been applied in the synthesis of (±)-debromoarborescidine B (**1b**), a derivative of naturally occurring arborescidine B (**1a**).[13] Compound **1b** possesses antiproliferative properties and it is significantly more potent than **1a**.[13a]

The synthesis was initiated with allylation of dihydrocarboline **27** under typical basic conditions to afford compound **28** (Scheme 4). Sequential, one-pot treatment of **28** with ethyl chloroformate to quaternise the imine functionality followed by indium-promoted allylation furnished diallylated compound **29**. Subsequent RCM, carried out with Grubbs' second generation catalyst, afforded product **30** in almost quantitative yield. The allyl to vinyl isomerisation was then carried out using the above discussed procedures. Although both methods afforded the expected product **31**, the process employing NaH as the base was shown to be more efficient. Finally, reduction of the carbamate functionality employing $LiAlH_4$ afforded the target compound, (±)-debromoarborescidine B (**1b**).

In conclusion, a mild method for *N*-allyl indole to *N*-vinyl indole double bond migration employing *t*-BuOK or NaH has been described. The reactions were carried out at room temperature affording the products in good yields, usually as *Z*/*E* mixtures, while the conditions tolerated a range of functional groups. The methodology was applied for the synthesis of (±)-debromoarborescidine B.

Acknowledgments

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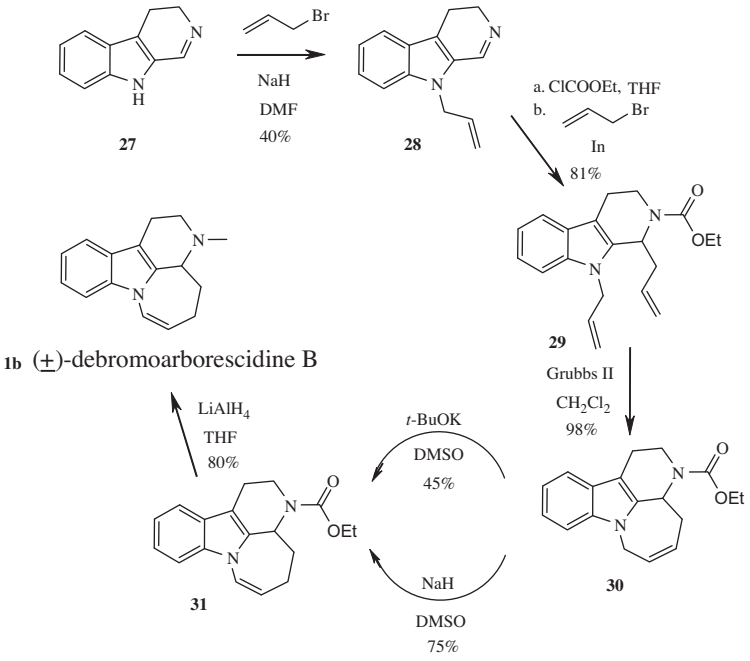

Scheme 4.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.069.

References and notes

1. (a) Ndagijimana, A.; Wang, X.; Pan, G.; Zhang, F.; Feng, H.; Olaleye, O. *Fitoterapia* **2013**, *86*, 35–47; (b) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2013**, *30*, 694–752; (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489–4497; (d) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532–547.
2. For selected recent examples, see: (a) Bennasar, M.-L.; Sole, D.; Zulaica, E.; Alonso, S. *Tetrahedron* **2013**, *69*, 2534–2541; (b) Manzo, E.; Pagano, D.; Carbone, M.; Ciavatta, M. L.; Gavagnin, M. *Arkivoc* **2012**, 220–228; (c) Crooke, S.; Whitlock, C. *Molecules* **2012**, *17*, 14841–14845; (d) Seetham Naidu, P.; Bhuyan Pulak, J. *Tetrahedron Lett.* **2012**, *53*, 426–428; (e) Bhat, V.; MacKay, J. A.; Rawal, V. H. *Tetrahedron* **2011**, *67*, 10097–10104; (f) Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706–1709; (g) Frebault, F. C.; Simpkins, N. S. *Tetrahedron* **2010**, *66*, 6585–6596.
3. Li, J. J.; Johnson, D. S.; Sliskovic, D. R.; Roth, B. D. *Contemporary Drug Synthesis*; Springer: New jersey, 2004. pp 161–187.
4. (a) England, D. B.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 2792–2802; (b) Schultz, A. G.; Malachowski, W. P.; Pan, Y. *J. Org. Chem.* **1997**, *62*, 1223–1229; (c) Belle, D. D.; Tolvanen, A.; Lounasmaa, M. *Tetrahedron* **1996**, *52*, 11361–11378; (d) Banim, M.; Pais, A. *J. Nat. Prod.* **1993**, *56*, 99–104; (e) Verpoorte, R. *J. Nat. Prod.* **1986**, *49*, 1–25.
5. For selected recent examples, see: (a) Verma, A. K.; Joshi, M.; Singh, V. P. *Org. Lett.* **2011**, *13*, 1630–1633; (b) Kabir, M. S.; Lorenz, M.; Namjoshi, O. A.; Cook, J. M. *Org. Lett.* **2010**, *12*, 464–467; (c) Ivachtchenko, A. V.; Frolov, E. B.; Mitkin, O. D.; Kysil, V. M.; Khvat, A. V.; Tkachenko, S. E. *Arch. Pharm.* **2009**, *342*, 740–747; (d) Liao, Q.; Wang, Y.; Zhang, L.; Xi, C. *J. Org. Chem.* **2009**, *74*, 6371–6373; (e) Mao, J.; Hua, Q.; Guo, J.; Shi, D.; Ji, S. *Synlett* **2008**, 2011–2016.
6. (a) Trofimov, B. A.; Vasiltsov, A. M.; Ushakov, I. A.; Ivanov, A. V.; Schmidt, E. Y.; Mikhaleva, A. I.; Protsuk, N. I.; Kobychev, V. B. *Mendeleev Commun.* **2007**, *17*, 296–298; (b) Abele, E.; Dzenitis, O.; Rubina, K.; Lukevics, E. *Chem. Heterocyc. Compd.* **2002**, *38*, 682–685; (c) Lebedev, A. Y.; Izmer, V. V.; Kazyulkin, D. N.; Beletskaya, I. P.; Voskoboynikov, A. Z. *Org. Lett.* **2002**, *4*, 623–626.
7. For a recent review, see: (a) Krompiec, S.; Krompiec, M.; Penczek, R.; Ignasiak, H. *Coord. Chem. Rev.* **2008**, *252*, 1819–1841; For recent selected examples, see: (b) Bujak, P.; Krompiec, S.; Malarz, J.; Krompiec, M.; Filapek, M.; Danikiewicz, W.; Kania, M.; Gebarowska, K.; Grudzka, I. *Tetrahedron* **2010**, *66*, 5972–5981; (c) Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. *J. Am. Chem. Soc.* **2010**, *132*, 7998–8009; (d) Morgans, G. L.; Ngidi, E. L.; Madeley, L. G.; Khanye, S. D.; Michael, J. P.; de Koning, C. B.; van Otterlo, W. A. L. *Tetrahedron* **2009**, *65*, 10650–10659; (e) Tsang, D. S.; Yang, S.; Alphonse, F.-A.; Yudin, A. K. *Chem. Eur. J.* **2008**, *14*, 886–894.
8. Jakel, C. Paciello, R. In *Asymmetric Catalysis on Industrial Scale*; Blaser, H.-U., Federsel, H.-J., Eds.; Wiley-VCH: Weinheim, 2010; pp 187–204.
9. For recent selected examples, see: (a) Im, G.-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933–17944; (b) Ohmura, N.; Nakamura, A.; Hamasaki, A.; Tokunaga, M. *Eur. J. Org. Chem.* **2008**, 5042–5045; (c) Zacuto, M. J.; Xu, F. *J. Org. Chem.* **2007**, *72*, 6298–6300.
10. (a) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *Chem. Rec.* **2007**, *7*, 238–253; (b) Arisawa, M.; Terada, Y.; Theeraladanon, C.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Organomet. Chem.* **2005**, *690*, 5398–5406; (c) Michalak, M.; Wicha, J. *Synlett* **2005**, 2277–2280; (d) van Otterlo, W. A. L.; Morgans, G. L.; Khanye, S. D.; Aderibigbe, B. A. A.; Michael, J. P. D. Billing, G *Tetrahedron Lett.* **2004**, *45*, 9171–9175; (e) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732–4734.
11. (a) Nova, A.; Ujaque, G.; Albeniz, A. C.; Espinet, P. *Chem. Eur. J.* **2008**, *14*, 3323–3329; (b) Otsuka, S.; Tani, K. *Synthesis* **1991**, 665–680; (c) Inoue, S.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 4897–4905; (d) Tani, K. *Pure Appl. Chem.* **1985**, 1845–1854; (e) Akutagawa, S.; Tani, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 146–161.
12. *General procedure for the t-BuOK promoted N-allyl to N-vinyl double bond migration:* A mixture of 1-allylindole (0.1 mmol), and *t*-BuOK (0.45 mmol, 4.5 equiv) in DMSO (3 mL) was stirred at rt. The reaction was monitored by TLC and when complete (1–3 h), Et_2O (30 mL) was added and the mixture was washed with H_2O (3 × 5 mL). The organic layer was then dried (Na_2SO_4) and the solid was separated by filtration. The filtrate was evaporated under reduced pressure and the oily residue was purified by column chromatography (SiO_2, petroleum ether/Et_2O) to afford the product.Spectral data for 2-iodo-*N*-[1-(1-propenyl-1*H*-indol-2-yl)but-3-enyl]benzamide (**14**): Isolated after column chromatography (SiO_2, 7:3 v/v petroleum ether–Et_2O) as a colourless solid (mp 127–129 °C) in 95% yield as a 2:1 mixture of *Z* and *E* isomers. IR: 3272, 1661, 1521, 1458, 739 and 716 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.57 (d, 3H, CH_3, *Z* isomer, *J* = 5.0 Hz), 1.97 (d, 3H, CH_3, *E* isomer, *J* = 6.5 Hz), 2.81–2.87 (m, 2H,=CHC*H*$_2$CH), 5.12–5.26 (m, 2H, C*H*$_2$= CHCH$_2$CH), 5.48 (q, 1uH, CH$_2$C*H*NH, *Z* isomer, *J* = 7.0 Hz), 5.60 (q, 1H, CH$_2$C*H*NH, *E* isomer, *J* = 7.0 Hz), 5.89–5.96 (m, 2H,=C*H*CH$_2$CHN*H*), 6.03–6.06 (m, 1H, CH$_3$C*H*=CHN, *Z* and *E* isomers), 6.55 (d, 1H, ArH), 6.74 (d, 1H, CH$_3$CH=C*H*N, *Z* isomer, *J* = 8.0 Hz), 6.86 (d, 1H, CH$_3$CH=C*H*N, *E* isomer, *J* = 14.0 Hz), 7.08–7.21 (m, 4H ArH), 7.33–7.34 (m, 2H, ArH), 7.50–7.59 (m, 1H, ArH), 7.85 (d, 1H, ArH, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1 (CH_3, *Z* isomer), 15.7 (CH_3, *E* isomer), 38.8 (=CHCH$_2$CH), 38.9 (=CHCH$_2$CH), 45.8, 46.2, 92.4, 100.5, 100.9, 110.9, 111.0, 118.7 (CH$_2$=CHCH$_2$CH), 120.1, 120.4, 120.5, 120.5, 122.2, 122.4, 123.6 (CH$_3$CH=CHN *Z* isomer), 124.3 (CH$_3$CH=CHN *E* isomer), 127.4, 127.7, 128.1, 128.2, 129.0,131.2, 133.6, 133.7, 136.7, 136.8, 138.8, 139.4, 140.1, 141.7, 167.9. *m*/*z*: 456 (M^+), 415, 281, 253, 231, 207, 168. HRMS (ESI): calcd for $C_{22}H_{21}IN_2O$ $(M+H)^+$: 457.07713 found: 457.07780.
13. (a) Santos, L. S.; Theoduloz, C.; Pilli, R. A.; Rodriguez, J. *Eur. J. Med. Chem.* **2009**, *44*, 3810–3815; (b) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org Lett.* **2005**, *7*, 1047–1050; (c) Santos, L. S.; Pilli, R. A.; Rawal, V. H. *J. Org. Chem.* **2004**, *69*, 1283–1289; (d) Korver, J.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron* **1998**, *54*, 6135–6146.