ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 3251–3253

www.rsc.org/chemcomm

COMMUNICATION

NMR evidence of the kinetic and thermodynamic products in the NIS promoted cyclization of 1-phenyl-4-pentenylamines. Synthesis and reactivity of *trans*-2-phenyl-5-iodopiperidines†

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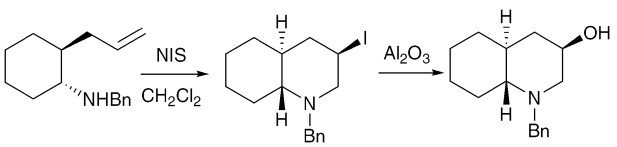
Received 22nd November 2010, Accepted 12th January 2011
DOI: 10.1039/c0cc05105e

The intramolecular reaction of secondary amines with tethered alkenes using NIS was studied, which gave insight into the kinetic *vs.* thermodynamic control of the iodoaminocyclization and the regioselectivity of the aziridinium ring-opening reactions, and led to functionalized piperidines.

Intramolecular alkene iodoamination is a classical tool for the synthesis of nitrogen-containing heterocycles.[1] Although amino-protected nucleophilic species (*e.g.* carbamates, amides) are common starting materials,[2] there is an ongoing interest in the use of free amines.[3] It is noteworthy that in the valuable cyclization of γ-aminoalkenes the nitrogen functionality has a great influence on the regioselectivity. Thus, the formation of a piperidine rather than a pyrrolidine ring when using amines contrasts with the exclusive 5-*exo* cyclizations observed when *N*-protected alkenylamines are employed.[2,4] Compounds originating from a formal 6-*endo* iodoaminocyclization are obtained either directly by isolation from the reaction medium, as in our reported 3-iododecahydroquinoline synthesis (Scheme 1),[3] or indirectly by a thermally induced ring-expansion of compounds initially generated by a 5-*exo* process.[5,6]

To gain insight into the iodoaminocyclization of γ-amino-alkenes, we undertook a study using 1-phenylpent-4-enylamines as starting materials and ^{1}H NMR to monitor the progress of the reaction. We herein report the obtained results as well as the behaviour of the formed compounds toward alumina, which shed light on the structure–reactivity relationship in the exchange process of β-iodoamines to β-aminoalcohols. The required amino alkenes **1(a–h)**[7] were synthesised by reductive amination



Scheme 1 Aminocyclization of *trans*-2-allylcyclohexylamines.

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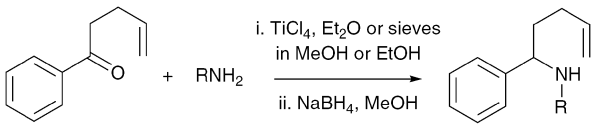
† Electronic supplementary information (ESI) available: Experimental procedures, analytical data and copies of ^{1}H and ^{13}C NMR spectra of all compounds. DOI: 10.1039/c0cc05105e

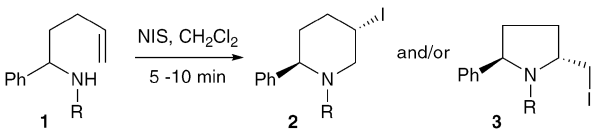


Scheme 2 Synthesis of pentenylamines **1**. **a**, R = Me (47%); **b**, R = Et (30%); **c**, R = Pr (75%); **d**, R = allyl (72%); **e**, R = Bn (71%); **f**, R = *i*Pr (71%); **g**, R = *c*Hex (78%); **h**, R = *t*Bu (64%).

of the 1-phenylpent-4-en-1-one[8] with the corresponding amines applying the reaction conditions depicted in Scheme 2.

With alkenylamines **1** in hand, we set out to explore their NIS-promoted cyclization mode. When using 1 equivalent of NIS and CH_2Cl_2 as the solvent, all the reactions were over in less than 1 h. Starting from **1a–e**, after removing the solvent, the NMR spectra of the crude reaction mixture exhibited signals belonging exclusively to the corresponding 5-iodopiperidines **2**, with the only by-product being succinimide. After filtration on a silica gel pad pure compounds were obtained in good yields (Table 1). However, when **1f** and **1g** were subjected to the same conditions a 6 : 1 mixture of piperidine **2** and pyrrolidine **3** was observed in each case. Nevertheless, after column chromatography only **2f** and **2g** were isolated in 63 and 55% yields, respectively. The amino alkene **1h** bearing the bulky *t*-butyl *N*-substituent led to pyrrolidine **3h**.

Table 1 Iodoaminocyclization of pentenylamines **1**[a]



R	Ratio **2**/ **3**[b]	Compound	Yield[c] (%)
Me	100/0	**2a**	75
Et	100/0	**2b**	70
Pr	100/0	**2c**	69
Allyl	100/0	**2d**	66
Bn	100/0	**2e**	79
*i*Pr	86/14	**2f**	63
*c*Hex	86/14	**2g**	55
*t*Bu	0/100	**3h**	50

[a] The reactions were also carried out in $CDCl_3$ in an NMR tube. [b] From ^{1}H NMR spectra of the crude. [c] After column chromatography.

We thought that this cyclization process (**1** → **2** *vs.* **3**) could be a useful tool to experimentally establish the course of the δ-alkenylamine iodoaminocyclizations. Thus, to control the olution of the starting material and time its complete conversion to **2**, we decided to carry out the reaction in an NMR tube. The ^{1}H NMR spectrum of a sample of **1** in $CDCl_3$ was recorded at rt, 1 equivalent of NIS was added, and the mixture was shaken for a few seconds before a second ^{1}H NMR analysis. In all cases the reaction was faster than expected, being over in 5–10 minutes. With **1a–e**, besides the previously obtained iododerivatives **2**, the initial spectra also revealed pyrrolidines **3a–e** as minor products. However, a few minutes later their corresponding signals had disappeared, as **2** was left alone. Pentenylamines **1f** and **1g** gave the same mixtures as reported above and our attempts to thermally rearrange **3f** to **2f** in $CDCl_3$ at 80 °C or in CD_3CN at 95 °C were unsuccessful.

Due to the speed of the iodoaminocyclization in $CDCl_3$, we switched to a less polar solvent for a better monitoring of the reaction. Luckily, using deuterated benzene allowed us to appreciate the evolution of the starting material **1** to pyrrolidine **3** and then the transformation of **3** to **2**. The NMR spectra (Fig. 1) clearly show that the conversion **1a** → **2a**, which was completed in 3 h, occurs through the intermediate **3a**. The first signals to appear after the addition of NIS to **1a** belonged to pyrrolidine **3a**, which was the main compound after 10 minutes. Piperidine **2a** signals began to show up after 15 minutes and increased with time, in contrast with those of **3a**. Within half an hour **3a** and **2a** were present in a ratio of 60 : 40 and after 3 h **2a** was the sole compound in the reaction mixture. This simple analysis demonstrated that the iodoaminocyclization reaction proceeds in a 5-*exo* fashion in a stereo- and regiocontrolled process yielding kinetically favoured pyrrolidine **3**, which then rearranges to the thermodinamically favoured piperidine **2** through an aziridinium intermediate. It was considered interesting from a synthetic standpoint to isolate pyrrolidines **3**. Starting from **1a**, the reaction was carried out in benzene itself, stopped at 3 min, and crude pyrrolidine **3a** was obtained by removing the benzene from the reaction medium at vacuum and room temperature. However, attempts to isolate this compound by a filtration over a silica gel pad rendered the enlarged compound **2a**. Additionally, we performed the reaction in $CDCl_3$ at −30 °C and as expected a sluggish iodoaminocyclization process was observed, leading to pyrrolidine **3a** in about 20 min. The compound was stable but quickly evolved into piperidine **2a** when the temperature was raised to 25 °C. Thus, the results clearly establish the low stability of **3** when it embodies a less sterically demanding *N*-substituent.

Additionally, the evolution of iododerivatives **2** on alumina was investigated. In all cases, after 1 night of adsorption on alumina, 2-hydroxymethylpyrrolidines **4** and/or 3-hydroxypiperidines **5** were isolated (Table 2). The results obtained clearly established the influence of the substituent at the nitrogen atom in the course of both reactions, iodoaminocyclization and conversion to alcohol derivatives. Thus, sterically undemanding *N*-substituents of **1a–e** allowed the piperidine derivatives to be isolated in a pure form in the cyclization process, but gave a mixture of five- and six-membered rings in the alcohol formation. In contrast, the more demanding *N*-substituents of **1f** and **1g** induced the partial formation of the pyrrolidine compounds in the cyclization but allowed the synthesis of pure piperidinol compounds **5f** and **5g**. The case of **1h** was different, since the bulky *t*-butyl group was responsible for the observed regioselective cyclization leading to the five-membered ring **3h** and its later transformation to **4h**.

An overview of the results (see Tables 1 and 2) shows that the regioselectivity of these processes arises from two factors: the

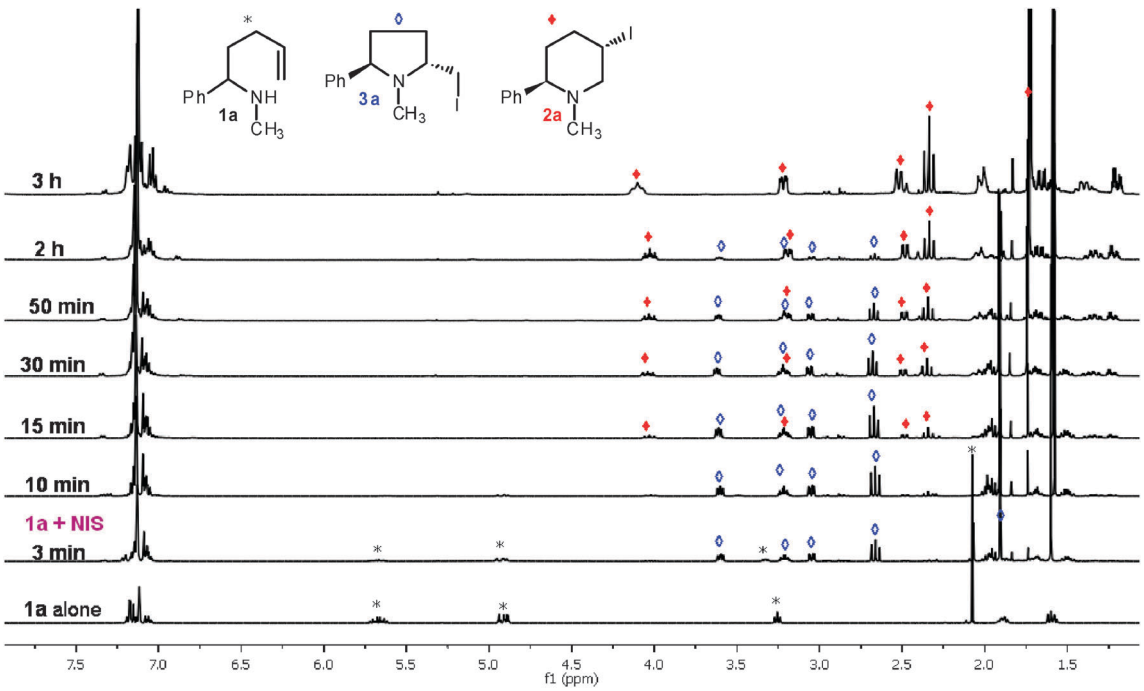
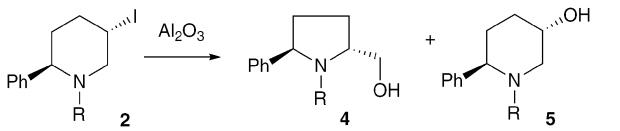


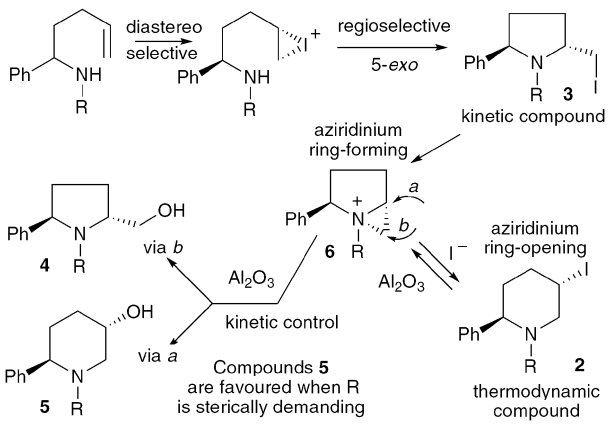
Fig. 1 ^{1}H spectra reaction monitoring of **1a** and NIS in C_6D_6.

Table 2 Evolution of iododerivatives **2** on alumina



R	Ratio **4**/ **5**	Yield[b] (%)
Me	**4a**/ **5a**: 66/34	88
Et	**4b**/ **5b**: 62/38	70
Pr	**4c**/ **5c**: 60/40	77
Allyl	**4d**/ **5d**: 60/40	89
Bn	**4e**/ **5e**: 57/43	86
*i*Pr	**4f**/ **5f**: 0/100	86
*c*Hex	**4g**/ **5g**: 0/100	95
*t*Bu	**4h**/ **5h**: 100/0[a]	60

[a] Starting from **3h**. [b] After column chromatography.



Scheme 3 Mechanism of formation of **2**, **3**, **4** and **5**.

nature of the *N*-substituent as well as the nucleophile. The mechanism involved in the formation of compounds **2–5** is depicted in Scheme 3. The more stable piperidines **2** generated from the initial pyrrolidine **3** can be explained by assuming a late transition state for the ring-opening of aziridinium compounds **6**, in which the attack of the iodide, a soft nucleophile, occurred at the methine carbon.[9] In contrast, in the irreversible Al_2O_3-promoted ring opening of **6** there is a mismatched structural trend, since the less substituted aziridinium carbon has an opposite counterpart effect on the substituent bulkiness at the nitrogen atom, generating steric crowding. Thus, in an early transition state the hard nucleophile did not exclusively give alcohols **4** (pathway b) by a regioselective attack at the methylene carbon,[10] which was hindered in the aziridinium intermediate **6**, and an increase of the attack ratio at the methine carbon giving piperidinol compounds **5** (pathway a) was observed, correlated with the steric demand of the *N*-substituent. The latter process is exclusive to the sterically encumbered aziridinium intermediates **6** generated from **2f** and **2g**, which embodies branched *N*-alkyl groups, leading to piperidines **5f** and **5g**, respectively.[11]

In conclusion, we have developed a straightforward method for the preparation of 5-iodo-2-phenylpiperidines by reaction of NIS with 1-phenylpent-4-en-1-amines. A better understanding of the iodoaminocyclization of δ-alkenyl amines has been achieved since a "slow motion" reaction was possible in deuterated benzene, allowing a direct observation of kinetic and thermodynamic products by NMR in the NIS-promoted cyclization. Thus, the formation of the thermodynamically favoured piperidine **2** *via* the kinetically favoured pyrrolidine **3** by a 5-*exo*-*trig* route was confirmed. The new data on the influence of the bulkiness of the substituent at the nitrogen on the regioselectivity of the kinetic aziridinium ring-opening are also noteworthy.[12]

This research was supported by the Ministry of Education and Science (Spain)-FEDER through project CTQ2007-61338/ BQU.

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