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Microwave-assisted aza-Prins reaction. Part 1: facile preparation of natural-like 3-azabicyclo[3.3.1]non-6-enes

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ABSTRACT

A facile and operationally simple route to diastereomerically pure, natural-like 3-azabicyclo[3.3.1]non-6-enes via microwave-assisted, $BF_3{\cdot}OEt_2$-promoted aza-Prins reaction has been developed. Complexity-generating transformations based on these products involving reactive functionalities introduced during the aza-Prins step have been developed.

Intramolecular cyclization of electrophilic iminium species onto an appropriately positioned olefin moiety (the aza-Prins reaction[1]) as a simple entry into pharmaceutically useful piperidines has been the subject of intense synthetic methodology research. From a review of the current literature, it appears that in most cases the cyclization is limited, with some exceptions, to *N*-sulfonyl homoallylic amines,[2] or requires activation of the olefin moiety by a trimethylsilyl substituent (the so-called aza-silyl-Prins reaction furnishing tetrahydropyridines[3]). The aza-Prins cyclization of *N*-tosyl homoallylamines with aldehydes (Scheme 1) has been catalyzed efficiently by a variety of Lewis [Fe^{III} halides,[2a,g] $BiCl_3$,[2b] GaI_3/I_2,[2c] I_2,[2f] Me_3SiI,[2h] $BF_3{\cdot}OEt_2$,[2i] $Sc(OTf)_3$[2k]] or Brønsted (phosphomolybdic acid,[2e] $HBF_4{\cdot}OEt_2$,[2j] TfOH[2l]) acids, and the initially generated carbocation has been trapped by the catalyst counterion,[2b,c,h,j] nucleophilic solvent molecule,[2i,l] water[2e] or even by a halide transferred from a halogenated solvent.[2a,d,g] A thorough investigation of the scope, mechanism, and limitations of the aza-Prins reaction has been undertaken by Dobbs.[4]

In an elegant total synthesis of (+)-nankakurines A and B, Overman demonstrated the utility of the aza-Prins cyclization involving cyclic unsaturated amines for constructing polycyclic piperidine-containing frameworks.[5] The skeletally related *Lycopodium* alkaloid, luciduline, has been constructed by Waters[6] via aza-Prins cyclization onto silyl enol ether. Inspired by these examples and motivated by the widespread presence of bicyclic piperidine moieties in natural products (Fig. 1),[7] we became interested in exploring the scope of this reaction using a model 3-cyclohexenylmethylamine **1**.

Compound **1** was easily synthesized in multigram quantities as shown in Scheme 2. Although the nitrile precursor to **1** can, in principle, be obtained directly from the cycloaddition of isoprene with acrylonitrile,[8] the same reaction with acrolein led to a greater yield and easier purification and therefore justified the two additional functional group interconversions.

After substantial experimentation on the reaction conditions (reaction medium as well as temperature regimens) and acid promoters, we discovered that pre-condensation of **1** with aromatic aldehydes or ethyl glyoxylate followed by microwave irradiation at 180 °C for 1 h in the presence of an equimolar amount of $BF_3{\cdot}OEt_2$ in 1,4-dioxane furnished, cleanly and efficiently (as judged by the LC–MS analyses of the reaction mixtures), hitherto undescribed 3-azabicyclo[3.3.1]non-6-enes **2a–k** (Scheme 3). Notably, the same reaction performed under conventional reflux in 1,4-dioxane led only to a slow conversion of **1** into a complex mixture of products. Similarly, an unsatisfactory result was obtained when the microwave-assisted cyclization was attempted in the presence of other Lewis acid promoters [$InCl_3$, $Sc(OTf)_3$, $FeCl_3$] that had been used by others[2] to promote the aza-Prins reaction of *N*-tosyl homoallylamine. This result appears to be in accordance with the failure of non-sulfonylated homoallylamines to give the aza-Prins cyclization products under $InCl_3$ catalysis as previously observed by Dobbs.[4]

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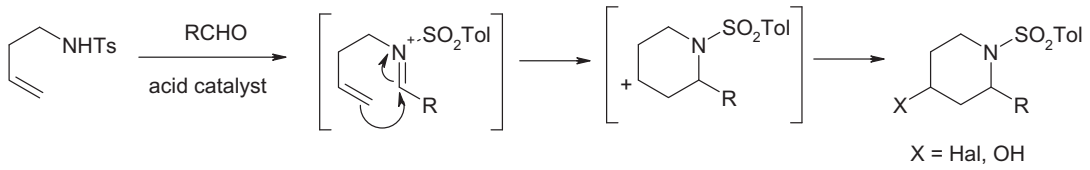


Scheme 1. aza-Prins cyclization involving *N*-tosyl homoallylamines.[2]

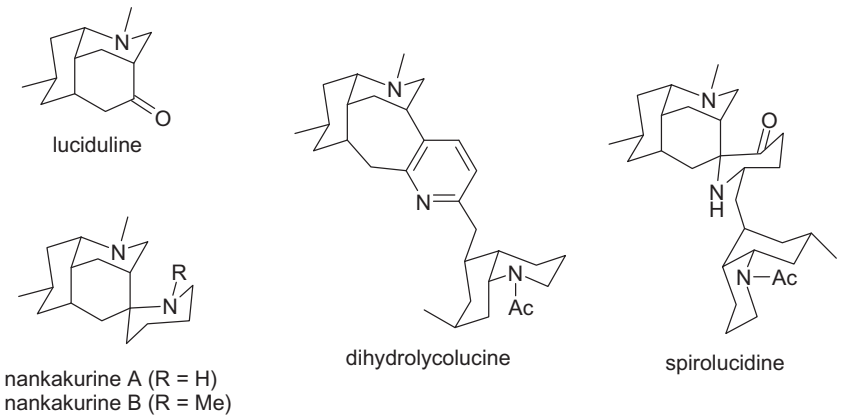
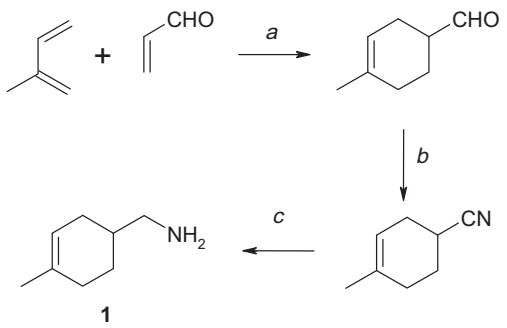
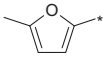
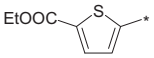


Figure 1. Examples of natural products containing bicyclic piperidine moieties.



Scheme 2. Synthesis of (±)-[(4-methylcyclohex-3-en-1-yl)methyl]amine (**1**). Reagents and conditions: (a) $ZnCl_2$ (5 mol %), neat, 40 °C, 18 h (76% after distillation); (b) NH_2OH/EtOH, rt, then $POCl_3/CH_2Cl_2$, reflux (81%); (c) LAH, 1,4-dioxane, reflux, 3 h (69%).

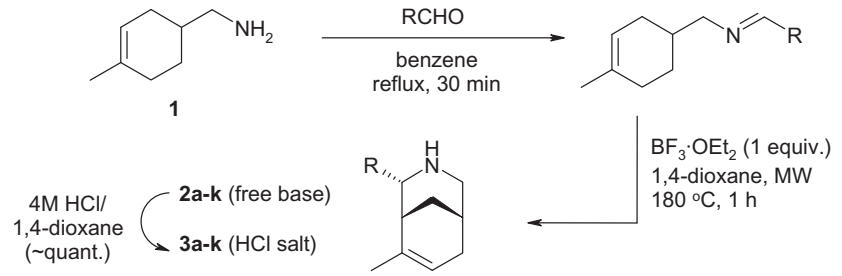
Table 1
3-Azabicyclo[3.3.1]non-6-enes **3a–k** prepared in this work

Product	R	Yield[a] (%)
3a	4-FC_6H_4	46
3b		67
3c	4-$MeOC_6H_4$	80
3d	4-ClC_6H_4	72
3e	4-$MeOOCC_6H_4$	64
3f	EtOOC	58
3g	2-HOC_6H_4	32
3h	3-Py	39
3i	Ph	70
3j	4-MeC_6H_4	81
3k		64

[a] Yield after chromatography and conversion into the hydrochloride salt.

Compounds **2a–k** were isolated chromatographically and converted, for easier handling, into the respective hydrochloride salts **3a–k** (Table 1).[9] All the products were obtained as a single *endo*-diastereomer, as confirmed by characteristic through-space interactions observed in their NOESY spectra (Fig. 2). Also notable was the fact that each product **2** was formed as a single double-bond regioisomer. This, as proposed earlier by Overman,[5] could be due to participation of the nitrogen atom in regiospecific intramolecular deprotonation of the initially formed carbocation intermediate **4** (Scheme 4).

Compounds **2**, albeit in lower yield, also formed on microwave irradiation of equimolar amounts of **1**, an aldehyde and $BF_3{\cdot}OEt_2$ in



Scheme 3. Microwave-promoted aza-Prins reaction toward 3-azabicyclo[3.3.1]non-6-enes.

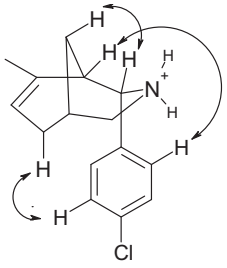


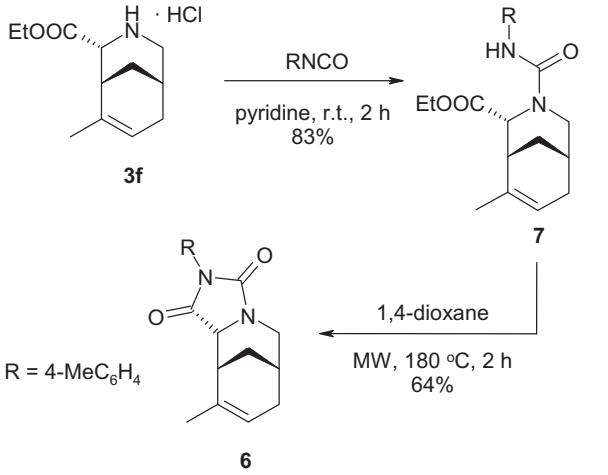
Figure 2. Through-space interactions observed in the NOESY spectrum of **3d**·HCl.

1,4-dioxane (i.e., without pre-formation of the Schiff base). In this reaction, the major products **2** were accompanied by a small (<10%) amount of 1-azaadamantane by-products **5**, presumably formed via a second aza-Prins reaction of **2** with unreacted aldehyde (Scheme 5). A similar access to the 1-azaadamantane framework was reported by Khuong-Huu.[10] Our further results describing the synthetic potential of double aza-Prins cyclization involving **1** as a facile entry into 1-azaadamantanes **5** are disclosed in the following communication.[11]

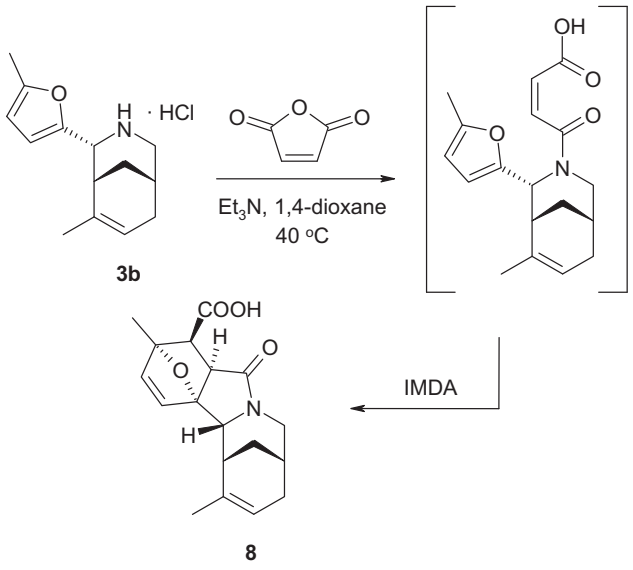
Compounds **2**(**3**) are of interest not only from the standpoint of their resemblance to naturally occurring alkaloids,[7] as well as fully synthetic, biologically active compounds (e.g., the recently described[12] carba-cytisine partial antagonists of the α4β2 neuronal nicotinic acetylcholine receptor which are potentially useful in smoking cessation). They contain a reactive nitrogen atom and can be viewed as a starting point en route to medicinally relevant scaffolds of increased complexity. This is exemplified by the synthesis of hydantoin compound **6** obtained via microwave-assisted cyclization of urea **7**, which was in turn obtained by carbamoylation of **3f** (Scheme 6). Another interesting example was provided by the acylation of **3b** with maleic anhydride which gave, on spontaneous intramolecular Diels–Alder (IMDA) reaction,[13,14] the structurally complex, polycyclic lactam carboxylic acid **8** (Scheme 7).

In conclusion, we have described the microwave-assisted, $BF_3{\cdot}OEt_2$-promoted aza-Prins reaction as a simple and diastereospecific entry to natural-like 3-azabicyclo[3.3.1]non-6-enes. With judicious choice of the peripheral groups, these compounds can serve as templates for further complexity-generating transformations.

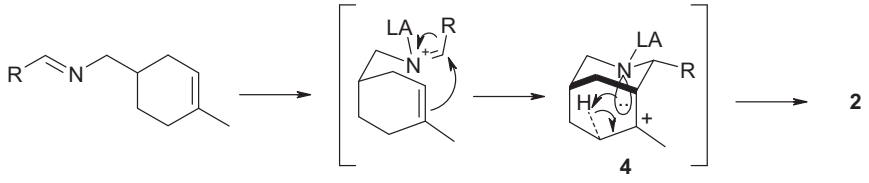
*Typical procedure—synthesis of compounds **3a–k**.* Equimolar amounts (2 mmol scale) of amine **1** and an aldehyde were combined in benzene and heated at reflux for 30 min. The mixture



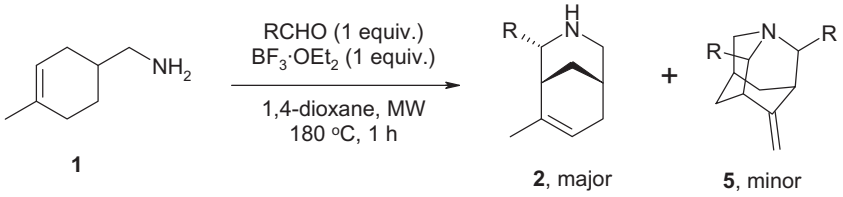
Scheme 6. Synthesis of tricyclic hydantoin **6**.



Scheme 7. Acylation of **3b** with maleic anhydride.



Scheme 4. Possible nitrogen atom contribution to the regioselective formation of **2**.



Scheme 5. Formation of 1-azaadamantane by-products in the aza-Prins reaction of **1** with various aldehydes.

was evaporated to dryness, the residue dissolved in anhydrous 1,4-dioxane (5 mL) and transferred into a microwave reactor tube. $BF_3{\cdot}OEt_2$ (1.0 equiv) was added, the reaction tube was capped with a septum and irradiated using a Biotage Initiator™ microwave reactor at 180 °C for 1 h. The solvent was evaporated and the residue was partitioned between $CHCl_3$ (10 mL) and 1 M aqueous NaOH solution. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, concentrated, and chromatographed on silica gel using an appropriate gradient of MeOH in CH_2Cl_2 as eluent. Fractions containing **2** (as verified by LC–MS analysis) were combined and concentrated in vacuo to give a viscous oil. This was dissolved in a minimum amount of 1,4-dioxane and treated with excess 4 M HCl in 1,4-dioxane. The resulting white crystalline precipitate was collected by filtration, washed with 1,4-dioxane and air-dried to provide analytically pure **3**.

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9. Characterization data for selected compounds: **3d**: ^{1}H NMR (400 MHz, 90 °C, DMSO-d_6) δ 10.60 (d, J = 11.0 Hz, 1H), 8.54 (d, J = 11.6 Hz, 1H), 7.45 (ABq, J = 10.9 Hz, 4H), 5.60 (s, 1H), 4.55 (d, J = 15.9 Hz, 1H), 3.13–3.38 (m, 3H), 2.33 (s, 2H), 2.20 (s, 1H), 2.09 (d, J = 16.0 Hz, 1H), 1.70 (d, J = 16.0 Hz, 1H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, 90 °C, DMSO-d_6) δ 135.6, 132.3, 129.9, 127.6, 127.5, 126.8, 59.5, 39.0, 29.6, 29.4, 23.2, 23.1; LC–MS (M−Cl) m/z 248.3. Anal. Calcd for $C_{15}H_{19}Cl_2N$: C, 63.39; H, 6.74; N, 4.93; found: C, 63.42; H, 6.78; N, 4.99; **3e:** ^{1}H NMR (400 MHz, 90 °C, DMSO-d_6) δ 10.61 (br s, 1H), 8.47 (br s, 1H), 7.95 (d, J = 10.7 Hz, 2H), 7.65 (d, J = 10.7 Hz, 2H), 5.65 (s, 1H), 4.61 (s, 1H), 3.87 (s, 3H), 3.09–3.35 (m, 3H), 2.20–2.40 (m, 3H), 2.12 (d, J = 16.6 Hz, 1H), 1.76 (d, J = 16.6 Hz, 1H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, 90 °C, DMSO-d_6) δ 165.5, 142.0, 130.1, 129.0, 128.5, 127.0, 126.0, 59.8, 51.4, 50.5, 39.0, 29.7, 23.2, 23.1; LC–MS (M−Cl) m/z 272.6. Anal. Calcd for $C_{17}H_{22}ClNO_2$: C, 66.33; H, 7.20; N, 4.55; found: C, 66.40; H, 7.27; N, 4.61; **3i:** ^{1}H NMR (400 MHz, 90 °C, DMSO-d_6) δ 10.46 (br s, 1H), 8.52 (br s, 1H), 7.47 (m, 2H), 7.29–7.37 (m, 3H), 5.58 (s, 1H), 4.52 (d, J = 15.1 Hz, 1H), 3.14–3.38 (m, 3H), 2.34 (br s, 2H), 2.18 (s, 1H), 2.10 (d, J = 15.8 Hz, 1H), 1.70 (d, J = 15.8 Hz, 1H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, 90 °C, DMSO-d_6) δ 137.2, 130.7, 128.1, 127.5, 126.9, 125.9, 60.1, 50.6, 29.9, 29.7, 23.9, 23.5; LC–MS (M−Cl) m/z 214.5. Anal. Calcd for $C_{15}H_{20}ClN$: C, 72.13; H, 8.07; N, 14.19; found: C, 72.02; H, 8.08; N, 14.09.
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