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Malte Leverenz, Guillaume Masson, Domingo Gomez Pardo, Janine Cossy. Synthesis of Azocanes from Piperidines via an Azetidinium Intermediate. Chemistry - A European Journal, 2021, 27 (66), pp.16325-16328. <10.1002/chem.202102739>. <hal-03773322>

HAL Id: hal-03773322

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Submitted on 17 Oct 2022

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Synthesis of Azocanes from Piperidines via an Azetidinium Intermediate

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Abstract: -Trifluoromethyl azocanes are accessible from 2-(trifluoropropan-2-ol) piperidines by metal-free ring-expansion involving a bicyclic azetidinium intermediate. The opening of the azetidinium intermediate was achieved by various nucleophiles (amines, alcoholates, carboxylates, phosphonates, halides and pseudo-halides) with an excellent regio- diastereo- and enantioselectivity and in good yields. The relative configuration of the piperidines and azocanes were assigned and the deprotected azocanes offer opportunities for further derivatization.

Eight-membered *N*-heterocyclic ring systems, e.g. azocanes and derivatives can be found in natural products such as otonecine,^[1] nakadomarin A,^[2,3] (+)-balasubramide^[4,5] or (±)- ϵ -clausenamide^[6] and in bioactive non-natural products such as trocimine, which can relieve chronic pain,^[7] or guanethidine, an adrenergic neuroblocking agent used against hypertension and glaucoma^[8] (Figure 1).

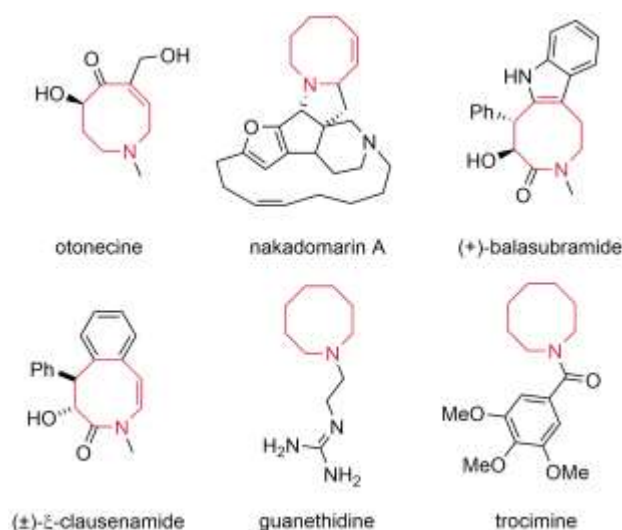
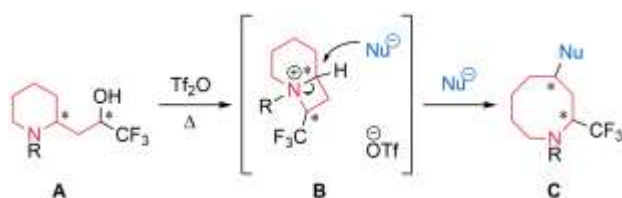


Figure 1. Examples of natural products and bioactive compounds featuring an eight-membered *N*-heterocyclic ring system.

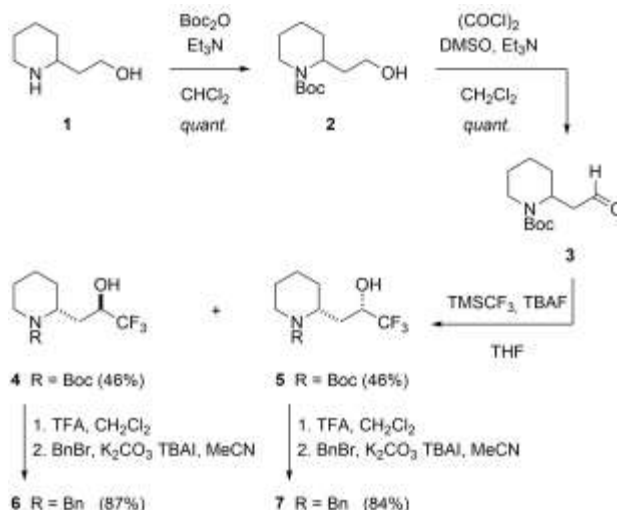
The access to medium-size rings is challenging due to unfavorable enthalpic and entropic barriers and transannular interactions during the formation of these medium size rings.^[9,10] The methods to access eight-membered *N*-heterocyclic systems are rare and most of the methods that have been developed are utilizing metals, such as transition metals which are expensive.^[11-19] Thus, free-metal methods to access eight-membered rings are attractive,^[20-25] particularly rearrangements as these processes are atom economic and efficient and do not involve expensive and scarce metals. Azocanes can be obtained from azetidines by using a [3,3]-sigmatropic rearrangement,^[26,27] or from various benzyl alcohol-tethered ynamides involving a stereoselective [1,3]-rearrangement.^[28] A ring-expansion of piperidine was used but the reaction is very limited and, in addition, the azocane was the minor compound, the major being the piperidine.^[29] As part of our program on diastereo- and enantioselective ring-expansion of *N*-heterocycles,^[30-37] we would like to report that piperidines **A** can be transformed to azocanes **C**, via an azetidinium intermediate **B**, with high regio- and diastereoselectivity. Functionalization of the azocanes at the C4 position provides opportunities to further alteration towards compounds of interest featuring an eight-membered *N*-heterocyclic ring system. In addition, due to the importance of a trifluoromethyl group on the bioactivity of molecules,^[38] we focused on the synthesis of substituted -trifluoromethyl azocanes, that can be considered as good bioisosters of eight membered-ring lactams (Scheme 1).



Scheme 1. Ring-expansion of piperidines **A** via bicyclic intermediates **B** to produce azocanes **C**.

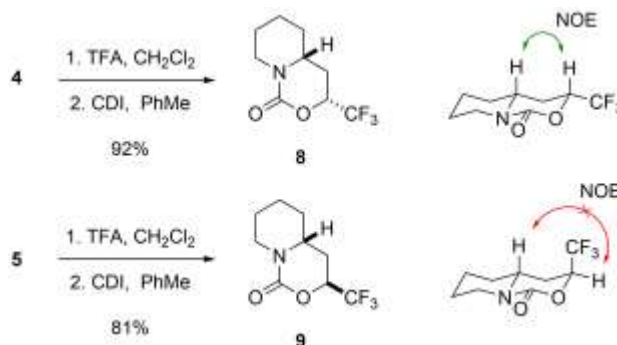
The racemic piperidines **A** were synthesized from the commercially available piperidine-ethanol **1**. The *N*-Boc-protection of the nitrogen and Swern oxidation of alcohol **2** gave aldehyde **3** in excellent yields and these two reactions were easily scalable. Applying the reaction conditions described by Prakash^[39,40] (TMSCF₃, TBAF, THF) produced a mixture of the two diastereomers **4** and **5** in a 1:1 ratio, which were separated by column chromatography. Both diastereomers were obtained in 46% yield (92% overall). However, to

access the bicyclic azetidinium intermediate **B**, the presence of a nucleophilic nitrogen is necessary. Thus, the carbamate of **4** and **5** was cleaved using trifluoroacetic acid (TFA) and the resulting amines were heated in the presence of benzyl bromide (TBAI, K_2CO_3 , CH_3CN) to produce the corresponding *N*-benzyl piperidines **6** and **7** (Scheme 2).



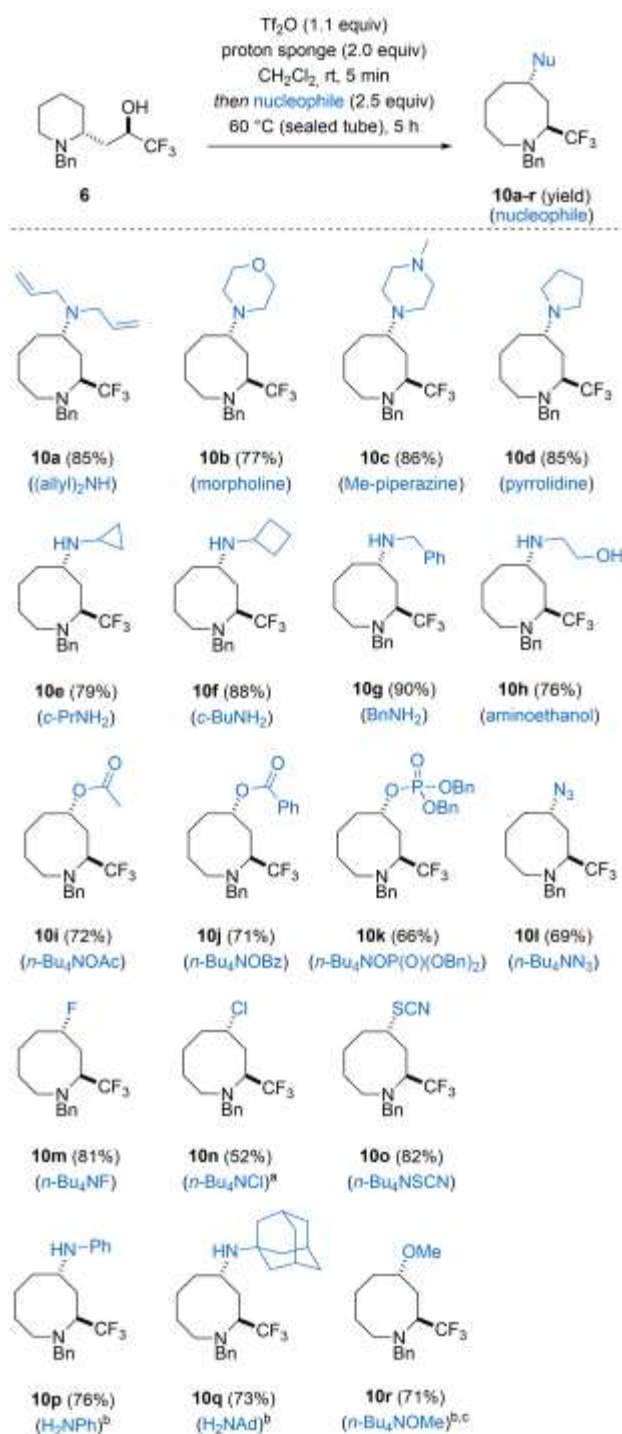
Scheme 2. Synthesis of benzyl-protected piperidines **6** and **7**.

In order to assign the relative stereochemistry of both diastereomers **4** and **5** and consequently **6** and **7**, the cleavage of the carbamate was achieved and the resulting amino-alcohols were cyclized with carbonyldiimidazole (CDI) to yield the cyclic carbamates **8** and **9**, which could be analyzed by NOESY NMR spectroscopy (Scheme 3).



Scheme 3. Synthesis of carbamates **8** and **9** and assignment of the relative configurations by NMR (NOESY) experiments.

Treatment of **6** with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 1,8-bis(dimethylamino)naphthalene (proton sponge) converted the alcohol to the triflate as a suitable leaving group (rt, CH_2Cl_2) and heating the reaction ($60\text{ }^\circ\text{C}$) allowed the formation of the azetidinium intermediate. Fortunately, in almost all cases the azetidinium intermediate could be formed in the presence of the nucleophile enabling a prompt ring-opening of the azetidinium intermediate by producing directly the azocanes **10** (Scheme 4).



Scheme 4. Ring-expansion of **6** to azocanes **10** induced by various nucleophiles. [a] Pre-formation of the azetidinium intermediate (60 °C, 4 h), then addition of *n*-Bu₄NCl, heating (60 °C, 3 h). [b] Reaction achieved in toluene at 120 °C. [c] 1.25 equiv *n*-Bu₄NOMe. Ad = adamantyl.

X-Ray diffraction of **10j** identified the relative stereochemistry of the substituents and confirmed the presumed *trans*-configuration of the azocanes synthesized from piperidine **6** (Figure 2). Comparison of the relative stereo-information at C2 and C4 of azocane **10j** with that of C2 and C2' of piperidine **6** confirmed the two consecutive and highly selective S_N2-type reactions during the formation and the opening of the azetidinium intermediates.

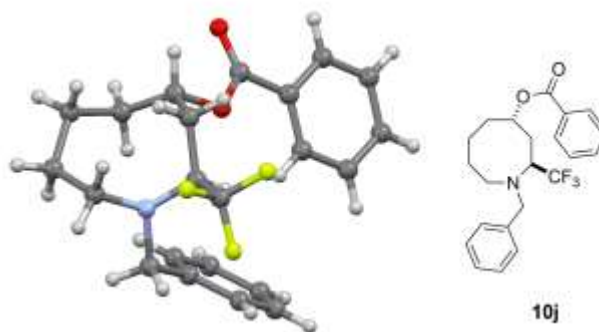
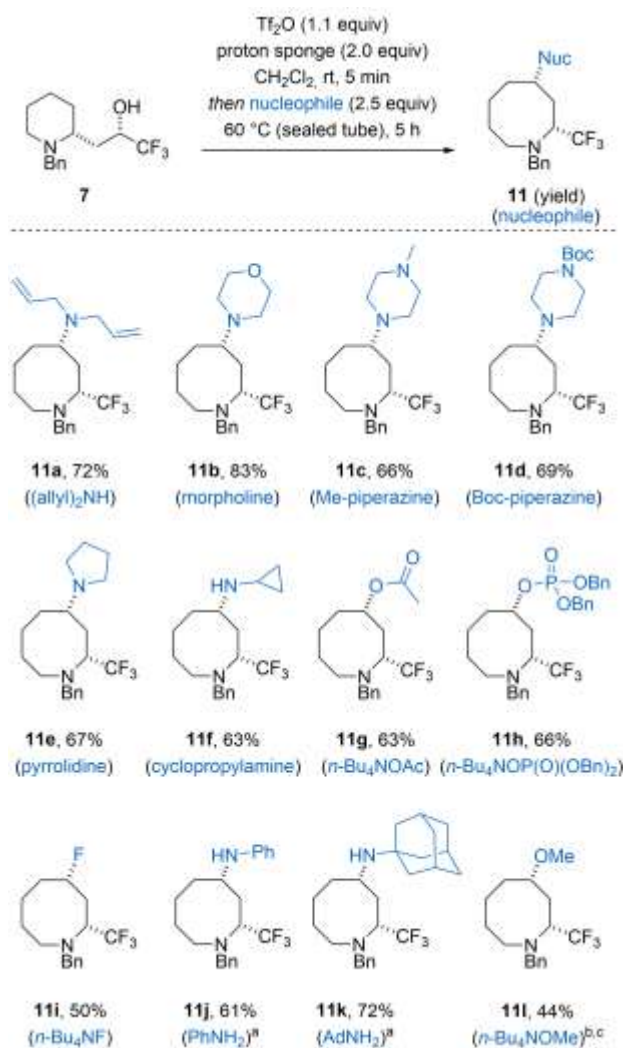


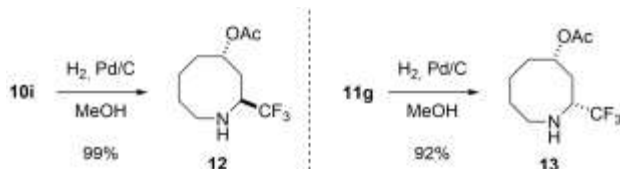
Figure 2. Relative configuration of azocane **10j** determined by single-crystal X-ray diffraction (CCDC 2094970).

The diastereomeric piperidine **7** was also treated under the same conditions as **6** with primary amines, secondary amines and different *n*-tetrabutylammonium salts as nucleophiles. The corresponding azocanes **11** were obtained in excellent diastereoselectivity (*dr* > 98:2) albeit in some cases with lower yields than to the ones obtained for azocanes **10** (Scheme 5).



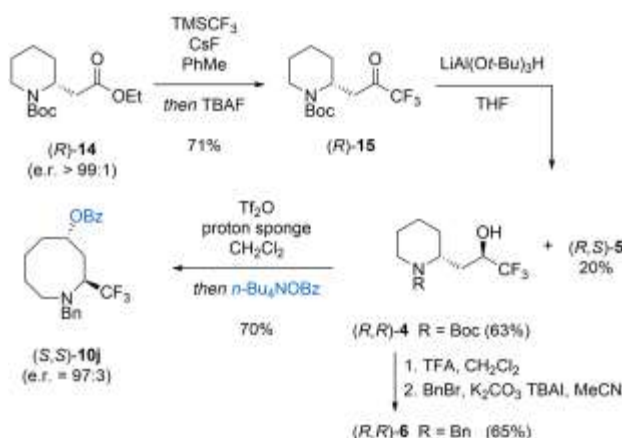
Scheme 5. Ring-expansion of **7** to azocanes **11** with various nucleophiles. [a] Reaction run in toluene at 120 °C. [b] Pre-formation of the azetidinium intermediate (120 °C, 2 h), then addition of *n*-Bu₄NOMe, heating (60 °C, 3 h). [c] 1.25 equiv *n*-Bu₄NOMe. Ad = adamantyl.

In an attempt to open up possibilities for post-functionalization at the nitrogen atom, we were able to perform a hydrogenolysis (H₂, Pd/C, MeOH) of the diastereomers **10i** and **11g**, which led to the deprotected azocanes **12** and **13** respectively with excellent yields and without any epimerization of the stereogenic center at the C2 position (Scheme 6).



Scheme 6. Synthesis of nonprotected azocanes **12** and **13** by debenzoylation.

As the biological activity of a compound is essentially linked to only one of the two enantiomers, we developed a strategy to access optically active -trifluoromethyl azocanes. Following an enzymatic kinetic resolution procedure,^[42,43] we prepared enantiomerically enriched piperidine (*R*)-**14** (see Supplementary Information), which was converted to the trifluoromethyl ketone (*R*)-**15** by the use of TMSCF₃ (Toluene, cat. CsF, TBAF). Reduction with LiAl(O*t*-Bu)₃H proved to be moderately diastereoselective and yielded (*R,R*)-**4** in 63% and (*R,S*)-**5** in 20% yield. Following the same procedures as previously for the protecting group interconversion to (*R,R*)-**6**, and the ring- expansion involving tetrabutylammonium benzoate as for the racemic material, we were able to obtain azocane (*S,S*)-**10j** in an optically active form (er = 97:3) (Scheme 7).



Scheme 7. Enantioselective synthesis of optically active azocane (*S,S*)-**10j**

In order to elucidate the importance of the trifluoromethyl group on the regioselectivity of the ring-expansion, the trifluoromethyl group was replaced by a methyl group in piperidine **6** and this latter was subjected to our standard reaction conditions using benzylamine as the nucleophile. However, the corresponding azocane could not be isolated but instead the piperidine where the hydroxy group has been displaced by the benzylamine, was obtained (see Supplementary Information). This proves that the trifluoromethyl group could not only have an effect on bioactivity but, in our case, is also necessary for a regioselective ring-expansion of a piperidine.^[30]

In conclusion, substituted piperidines can be a good source of azocanes, if a bicyclic

azetidinium intermediate can be formed. This latter can be opened by a diversity of nucleophiles regio- and stereospecific when enantiomerically enriched piperidines are involved in the ring-expansion process, optically active azocanes can be obtained creating new possibilities for medicinal chemists to further explore the chemical space.

Acknowledgements

E. Brohan, C. Prevost, S. Sablé from Sanofi are thanked for their help in the determination of the enantiomeric excess of (S,S)-**10j**.

Keywords: Azocanes • Heterocycles • Ring expansion • Fluorine • Azetidinium

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