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Synthesis and reactivity of enantiomerically pure *N*-alkyl-2-alkenyl azetidinium salts

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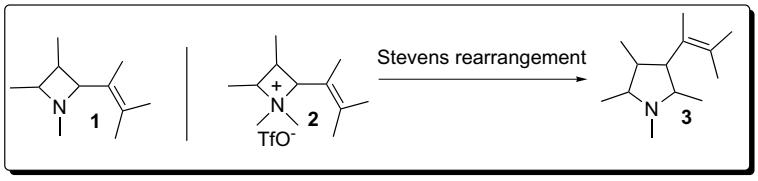
Abstract—A synthesis of stereodefined enantiomerically pure 2-alkenyl azetidines is described using Wittig olefination as key step. The quaternary triflate ammonium salts of these heterocycles were prepared in a stereoselective way and treatment of these azetidinium salts with a base (KHMDS or PhLi) induced a regioselective Stevens rearrangement leading to a 3-alkenyl pyrrolidine. An unprecedented S_N2' reaction involving phenyllithium as nucleophile and an ammonium as leaving group was observed in one case.

In the course of studies on the synthesis and reactivity of non-racemic azetidines,[1] we wish to report herein a convenient synthesis of stereodefined enantiomerically pure *N*-alkyl-2-alkenyl azetidines of general structure **1**, which, to our knowledge, have not been reported to date.[2] Preliminary investigations on the reactivity of these strained cyclic allylamines were aimed in order to induce ring expansions[1e,3] of these compounds that could eventually be used as key steps for the stereoselective synthesis of larger nitrogen heterocycles.

This work describes a regioselective Stevens rearrangement performed on the azetidinium triflate derivatives **2** of these heterocyles, leading to 3-alkenyl pyrrolidines **3**, and delineates the suitable experimental conditions and stereochemical requirements in **2** needed to induce this reaction.

2-Alkenyl azetidines **13**–**19**, showing different substitution pattern on the heterocycle and on the alkene moiety were all prepared in good yields starting from the corresponding 2-cyano azetidines, for which we recently described an efficient synthesis starting from enantiomerically pure β-amino alcohols.[1a] The key step for the alkene formation involves a Wittig olefination performed either on ketones **8**–**10** or on epimeric aldehydes **11**–**12** to afford 2-alkenyl azetidines **13**–**18**.

The ketones were prepared by addition of an organolithium reagent onto the nitrile moiety, as previously described,[1c] whereas aldehydes **11** and **12** were produced by Swern oxidations of the corresponding primary alcohols **6** and **7**. Gratifyingly, these aldehydes were produced without any detectable epimerization, though α-amino aldehydes are known to have low configurational stabilities.[4] This can be attributed to the strain of the four-membered ring, that disfavors the formation of an enol.[5] Unsaturated (*E*) ester **13** was stereoselectively prepared in a one-pot (Swern + Wittig) sequence from **7**, and needed to be purified immediately after



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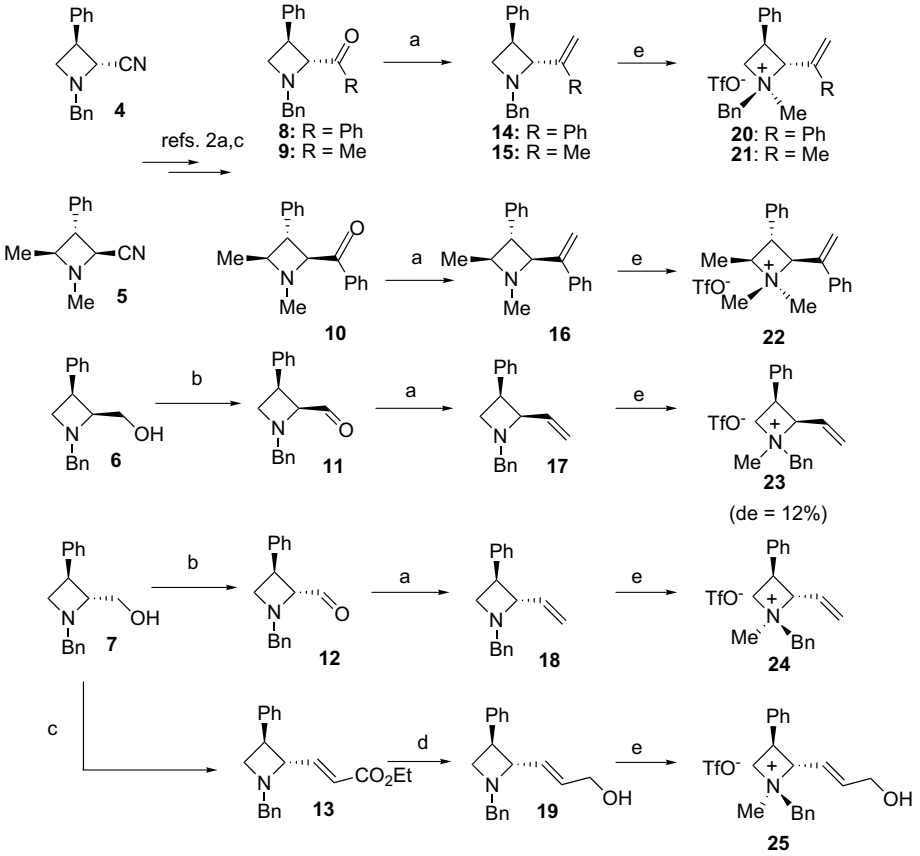
the reaction, since a partial isomerization of the alkene into the (*Z*) isomer was observed with stored crude samples of **13**. Finally, reduction of **13** with DIBAH gave allylic alcohol **19**. It should be mentioned however that a hindered ketone (**8**: R = *t*-Bu) failed to give the corresponding alkene upon a trial of Wittig olefination (Scheme 1).

Having in hand a different set of alkenyl azetidines, the ammonium triflate salts of these heterocycles were next prepared upon reaction with methyltrifluoromethanesulfonate.[6] In all cases, except for the 2,3-*cis* compound **17** leading to ammonium **23**, this alkylation proceeded in a highly diastereoselective way, and gave ammoniums **20**–**25** depicted in Scheme 1. In order to induce a Stevens rearrangement in these compounds, diastereoisomerically pure *N*-benzyl triflates **20**, **21**, **24**, and **25** were then treated at −78 °C with KHMDS or PhLi in THF and gave pyrrolidines **26**–**29**, in fair (unidentified minor by products were produced starting from **20**) to good yields, resulting from a regioselective rearrangement. These compounds were obtained as mixtures of isomers at C-2, which could be separated by flash chromatography. When the mixture of ammonium isomers **23** resulting from the reaction of **17** with MeOTf was treated with KHMDS, a more complex mixture of at least four different products was formed (Table 1).

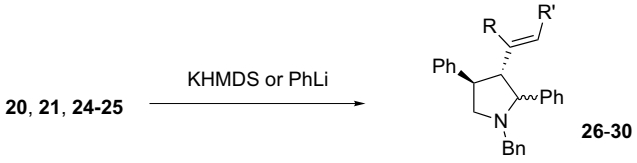
The results presented above deserve some comments. First, the high stereoselectivity observed during the formation of the trifluoromethanesulfonates starting from *trans*-*N*-benzyl-2,3-substituted azetidines **14**, **15**, **18**, and **19** can be rationalized by considering the four different conformers and invertomers **A**–**D** of the azetidine ring depicted in Scheme 2. Among these, conformer **C** appears to be the more stable since all the substituents on the ring are in a pseudo-equatorial position. Furthermore, the lone pair of the nitrogen atom is not sterically crowded for the subsequent alkylation. The selectivity can therefore be explained by the favored alkylation of this conformer. On the opposite, when 2,3-*cis* compound **17** is considered, conformational analysis does not clearly show that one among the four conformers is more stable or reactive compared to the other ones. In this case, the alkylation probably proceeds on several conformers, which can explain the low diastereoselectivity observed for the alkylation of **17**.

The Stevens rearrangement of ammonium ylides has been studied in much detail and was described once involving azetidinium substrates.[7] It is admitted that this rearrangement occurs through diradical species in a solvent cage, after formation of an intermediate ammonium ylide. It is also known that configuration of the carbon migrating center is retained.[8] The outcome of

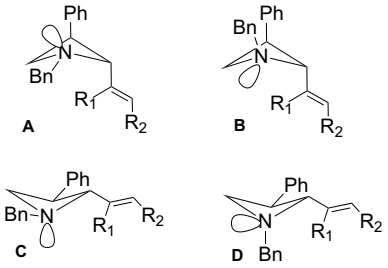


Scheme 1. Reagents and conditions: (a) trimethylphosphonium iodide, BuLi, −78 °C, THF, 79% (**14**), 62% (**15**), 86% (**16**), 62% from (**6**), (**17**), 67% (**18**); (b) Swern oxidation, 93% (**12**); (c) Swern oxidation, then $(C_6H_5)_3PCH{=}CHCO_2Et$, 84%; (d) DIBAH, THF, −78 °C, quant.; (e) MeOTf, DCM, 0 °C, 93% (**20**), 83% (**21**), 94% (**22**), quant. (**23**), 98% (**24**), 95% (**25**).

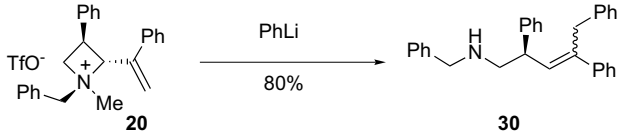
Table 1. Reaction of 2-alkenyl azetidinium triflates in basic medium



Substrate	Conditions	Product	Yield (%)	de (%)
20	KHMDS	**26** (R = Ph, R′ = H)	39	8
21	KHMDS	**27** (R = Me, R′ = H)	94	72
24	KHMDS	**28** (R = H, R′ = H)	83	6
25	PhLi	**29** (R = Ph, R′ = CH_2OH)	69	8



Scheme 2. Conformational analysis for 2,3-*trans* azetidines.



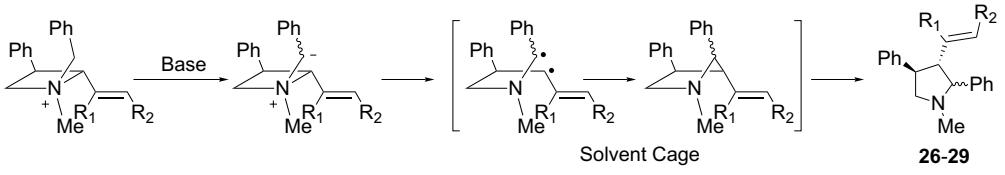
Scheme 4. Unexpected ring opening occurs with compound **20**.

the reaction described herein fits well with these points: the high chemoselectivity of deprotonation at the benzylic center and the total regioselectivity of the migration involving the carbon bearing an alkenyl moiety accounts for the production of two isomeric pyrrolidines at C-2. This low diastereoselectivity might be the result of a non-selective deprotonation (formation of *Z* and *E* intermediate ylides) at the methylene carbon of the benzyl group (Scheme 3).

Altogether, the reaction occurs very rapidly at low temperature, is unsensitive to the substitution pattern of the alkene present in the substrate and gives no β-elimination product. The nature of the employed base is, however, important: while KHMDS worked well in all cases, phenyllithium, frequently used as a base in similar reactions,[7] gave erratic results: it afforded the rearrangement product in case of **25**, but extensive degradation was observed with substrates **21** and **24** and a surprising outcome was obtained with **20**. In this last case, S_N2' addition of the organolithium reagent occurred on the alkene, resulting in an opening of the azetidine to give **30** (Scheme 4).

This reaction was unexpected since nitrogen-derived moieties have scarcely been used as leaving groups in S_N2' reactions involving organometallic reagent and are restricted to particular cases in which the leaving group ability of the nitrogen atom is increased by strain release such as in 2-vinyl-[9a] or 2-ethynyl-[9b] *N*-tosyl aziridines. This is the case here, with the strain of the azetidine ring, but to our knowledge, ammonium acting as leaving group in S_N2' processes involving organometallic nucleophiles has no precedent.[10] Interestingly, alkene **30** is produced as a single isomer, whose configuration was not determined. It should be noted that this reaction occurred only with ammonium **20**, in which the double bound is substituted by a phenyl group. This can give some insights into the mechanism of this reaction that might create a transient partial negative charge on the alkenyl carbon, which is stabilized in case of substrate **20** by the aromatic ring.

The relative stereochemistries of the ammonium salts **20**–**21** and **24**–**25**, that is a *trans* relationship between the *N*-benzyl substituent and the adjacent alkenyl moiety, were determined by NMR using a NOESY experiment performed with **21**. Indeed, **20**, **24**, and **25** display the same 2,3-*trans* substitution pattern on the azetidine ring as in **21**, and the alkylation step producing these compounds is expected to proceed with the same stereoselectivity. It should be noted that because of the



Scheme 3. Mechanism of the Stevens rearrangement of azetidines **20**, **21**, **24**, **25**.

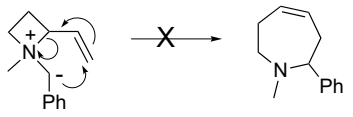


Figure 1.

low conformational mobility brought by the four-membered ring, this *trans* disposition between the ylide and the alkene precludes the possibility of a[2,3] sigmatropic shift (Fig. 1) that would produce a tetrahydroazepine.[11] The more complex mixture obtained with ammoniums **23**, in which the ylide is in part *cis* to the alkene, suggest that this process might be operative and highlight the importance of the relative configuration of the substituents in the starting azetidine for the success of the Stevens rearrangement.

In summary, we have decribed herein a synthesis of enantiomerically pure 2-alkenyl azetidines and a regioselective Stevens rearrangement of their ammonium derivatives. Further work is in progress in our group in order to delineate the scope of these reactions.

Acknowledgements

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