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Tetrasubstituted Pyrrolidines via a Tandem Aza-Payne/Hydroamination Reaction

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Hydroamination reactions of alkenes and alkynes have received considerable attention in the recent literature.[1] While the hydroamination of alkynes is facile compared to that of the corresponding alkenes, many alkyne hydroamination protocols require the use of metal catalysts or rigorously anhydrous or anaerobic conditions. Functional group tolerance often poses a particular problem in expanding hydroamination protocols to the preparation of synthetically useful building blocks. Hydroamination methods that do not involve the use of transition metals are not as well developed, but strong bases or bases containing electropositive metals have been reported to give alkyne hydroamination, especially when the nucleophilic nitrogen is in the form of an amide or sulfonamide.[1d,e,2] However, the use of highly functionalized precursors has traditionally been avoided, as the strongly basic conditions can often lead to unwanted side reactions.

We report a mild tandem aza-Payne/hydroamination reaction of aziridinols mediated by dimethylsulfoxonium methylide that yields highly functionalized pyrrolidine ring systems in one pot at room temperature (Scheme 1). The resulting strained enamide products are potentially useful synthons for the rapid construction of densely substituted pyrrolidines and pyrrolidinones for use in natural product synthesis.[3]

The aziridinol substrates were synthesized from the corresponding aziridine aldehydes according to a previous report describing a chelation-controlled addition of Grignard reagents to Boc-protected aziridine aldehydes.[4] Addition of Grignard or organolithium reagents to a series of *N*-tosylated aziridine aldehydes gave the desired alcohols in good yields. The presence of an R group *syn* to the carbonyl eroded the diastereoselectivity (**1a** and **1o**, Table 1), while the use of a *trans* disubstituted aziridine aldehyde gave only moderate *dr* (**1b** and **1c**). However, the use of 2,2,3-trisubstituted aziridine aldehydes gave the *syn*-aziridinols as the sole detectable product (Table 1, **1d**−**1m**). Also of note was the excellent diastereoselectivity obtained in the generation of quaternary hydroxyl centers from aziridine ketones (**1j** and **1k**). The presumed chelation-controlled process with tosyl-protected aziridines is in doubt with the excellent *dr*'s obtained with the 2,2,3-trisubstituted aziridines; this is the subject of ongoing studies (addition of excess TMEDA as a chelating agent had no effect on the *dr* of the reaction). The *syn* relationship between the aziridine and the alcohol was verified by X-ray crystallography of **2d** and **2h** (see Supporting Information).

The high diastereoselectivity obtained in the addition of Grignard reagents to the aziridine aldehydes was crucial to the success of the hydroamination. As shown in Scheme 2, only the *syn* diastereomer underwent hydroamination, as the aza-Payne rearrangement[5] orients the anionic nitrogen and the alkyne on the same side of the epoxide. The *anti* diastereomer undergoes the aza-Payne rearrangement, but cannot cyclize to the pyrrolidine.

The hydroamination reaction was initially performed by treating the epoxy amine **4d** with 8.0 equiv of dimethylsulfoxonium methylide and heating the reaction to 80 °C overnight. The product

Scheme 1

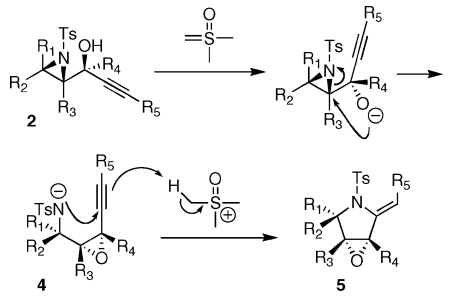
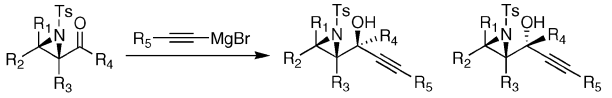


Table 1. Preparation of Aziridinol Substrates[a]



	1a-o				**2a-o**; *syn*		**3a-o**; *anti*
	R_1	R_2	R_3	R_4	R_5	yield	**2:3**
a	CH_3	CH_2OBn	H	H	H	56%	1:1
b	H	C_7H_{15}	H	H	H	67%	2.8:1
c	H	CH_2OBn	H	H	H	71%	2:1
d	H	CH_2OBn	CH_3	H	H	96%	>97:3
e	H	Ph	CH_3	H	H	90%	>97:3
f	H	*p*MeOPh	CH_3	H	H	67%	>97:3
g	H			H	H	93%	>97:3
h	H	CH_2OBn	CH_3	H	CH_3	92%	>97:3
i	H	CH_2OBn	CH_3	H	Ph	91%	>97:3
j	H	CH_2OBn	CH_3	CH_3	H	89%	>97:3
k	H	CH_2OBn	CH_3	CH_3	Ph	84%	>97:3
l	H	CH_2OBn	CH_3	H	TMS	90%	>97:3[b]
m	H	CH_2OBn	CH_3	H	TIPS	98%	>97:3[b]
n	H	CH_2OBn	CH_3	C_2H	H	80%	---
o	*n*Bu	CH_3	CH_3	H	H	73%	1.2:1

[a] A 0.028 M solution of the aldehyde in dichloromethane was cooled to −78 °C and treated with 5 equiv of the Grignard reagent. [b] Lithium acetylide was used to prepare the alcohol.

pyrrolidine **5d** (Table 2) was obtained in 99% yield. However, we found dimethylsulfoxonium methylide to be an effective base for the aza-Payne rearrangement, and thus, a one-pot conversion of aziridinols to tetrasubstituted pyrrolidines was developed (Table 2).[6] The substrates were treated with an excess of ylide (2−4 equiv) and stirred at rt to yield the desired pyrrolidines in moderate to good yields. For **2a** and **2c**, the desired *syn*-aziridinol substrate could not be cleanly separated from the *anti* byproduct. Thus, prior treatment of **2a** and **2c** with NaH in THF gave mixtures of the epoxy amines, which were separated by column chromatography, and the desired diastereomer was subjected to hydroamination conditions. Alternatively, the hydroamination could be run on the mixture of *syn*/*anti* compounds, and the epoxy amine (resulting

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Scheme 2

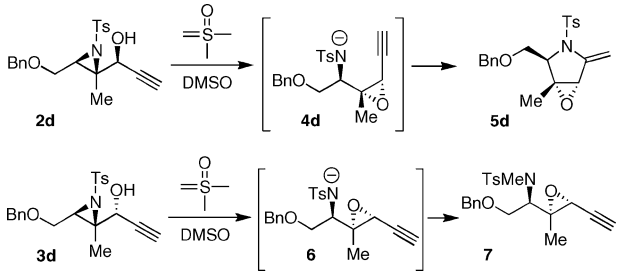
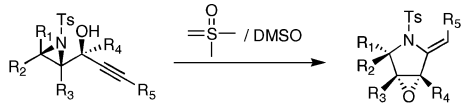


Table 2. One-Pot Conversion of Aziridinols to Pyrrolidines[a]



SM	R_1	R_2	R_3	R_4	R_5	pdt	yield
2a	CH_3	CH_2OBn	H	H	H	**5a**	72%[b]
2b	H	C_7H_{15}	H	H	H	**5b**	82%
2c	H	CH_2OBn	H	H	H	**5c**	73%[b]
2d	H	CH_2OBn	CH_3	H	H	**5d**	76%
2e	H	Ph	CH_3	H	H	**5e**	71%
2f	H	*p*MeOPh	CH_3	H	H	**5f**	71%
2g	H			H	H	**5g**	65%
2h	H	CH_2OBn	CH_3	H	CH_3	**5h**	0%[b]
2i	H	CH_2OBn	CH_3	H	Ph	**5i**	63% *Z*:*E* 14.5:1
2j	H	CH_2OBn	CH_3	CH_3	H	**5j**	64%
2k	H	CH_2OBn	CH_3	CH_3	Ph	**5k**	69% *Z*:*E* 14:1
2l	H	CH_2OBn	CH_3	H	TMS	**5d**	68%
2m	H	CH_2OBn	CH_3	H	TIPS	**5m**	0%
2n	H	CH_2OBn	CH_3	C_2H	H	**5n**	28%
2o	*n*Bu	CH_3	CH_3	H	H	**5o**	57%

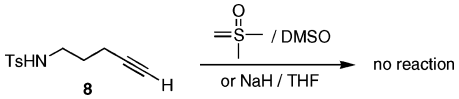
[a] The aziridinols (0.1 M in DMSO) were treated with 4.0 equiv of dimethylsulfoxonium methylide (prepared from Me_3SOI and NaH in DMSO) and stirred at rt. [b] Yield starting from the epoxy amine.

from reaction of the *anti* diastereomer) was separated from the desired pyrrolidine (**2o**). The remaining substrates (**2b**, **2d**−**2n**) contained only the *syn*-aziridinol, and the majority underwent hydroamination smoothly. The exceptions were alkynes substituted with alkyl or silyl groups (Table 2, **2h**, **2l**, and **2m**). It may be necessary for terminally substituted alkynes to contain a group capable of stabilizing a developing negative charge on the carbon adjacent to the newly forming C−N bond. The TMS-substituted alkyne **2l** did deliver the desilylated product **5d**, presumably as a result of initial deprotection of the TMS group. The *Z*-stereochemistry of the enamides obtained from aryl-substituted alkynes (**2i** and **2k**) may result from prior coordination of the sulfoxonium to the opposite face of the alkyne, thus leading to rapid proton transfer and the observed stereochemistry.

The hydroamination reaction can be run catalytically in ylide, but the aza-Payne rearrangement requires an excess (2−4 equiv) of ylide to proceed with good conversion. A 64% yield of **5d** was obtained from the epoxy amine **4d** using 0.2 equiv of ylide. Further studies are ongoing to find conditions that allow the aza-Payne rearrangement to proceed using only a catalytic amount of base.

We suspected this facile hydroamination was aided by the preorientation of the nitrogen and the alkyne on the same side of the

Scheme 3



epoxide by the aza-Payne rearrangement (Scheme 2). An unfunctionalized amino alkyne (**8**) was subjected to hydroamination conditions (Scheme 3), but no pyrrolidine product was obtained under several different conditions, implying a decrease in activation entropy of the cyclization is the underlying reason for the favorable hydroamination reaction.[7]

In conclusion, we have demonstrated a mild, base-mediated tandem aza-Payne/hydroamination reaction that yields a highly functionalized pyrrolidine ring system in the form of a strained enamide. Further studies are underway to expand the scope and mechanism of this hydroamination. Elaboration of the products into useful synthons for natural product synthesis is also currently under examination.

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Supporting Information Available: Experimental procedures and spectral information is available for compounds **1a**−**o**, **2a**−**o**, and **5a**−**o**, as well as coordinates for the X-ray crystal structures of **2d** and **2h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The use of other bases, such as NaH in THF or DMSO, or Grignards was unsuccessful in yielding the pyrrolidine products, and instead delivered the aza-Payne rearranged epoxy amines. Presumably, the protonated ylide (ylide used as the base) functions as a proton source during the hydroamination of the alkyne.

(7) (a) Winnik, M. A. *Chem. Rev.* **1981**, *81*, 491−525. (b) Page, M. I.; Jencks, W. P. *Proc. Nat. Acad. Sci. U.S.A.* **1971**, *68*, 1678−1683.

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