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Readily Available Unprotected Amino Aldehydes

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Continuing interest in stereochemically complex natural products and natural product-inspired synthetic molecules requires processes that minimize protection/deprotection sequences on incompatible functional groups. Identification of such reactions, especially in complex heterocycle synthesis, would facilitate discovery of bioactive molecules. Herein we report a new class of bench-stable compounds that contain seemingly incompatible functional groups: an aldehyde and an unprotected secondary amine.

Unveiling the secondary amine functionality in the presence of an aldehyde is typically done when an instant condensation resulting in an iminium/enamine system is desired.[1] It is difficult to see how an unprotected secondary amine could coexist with an aldehyde in the same molecule for a prolonged period of time.[2,3] Autoprotection of the amine by protic acid has been employed in order to stabilize labile primary amino aldehydes, although they were found to be susceptible to self-condensation above pH 5.[4] The possibility of self-condensation can be suppressed, but it requires incorporation of a quaternary α-carbon.[5] Using an unprotected aziridine as a secondary amine we considered the possibility that a thermodynamic driving force to undergo condensation could be offset by a high barrier imposed on this process by the aziridine ring strain (Figure 1).[6] As a result, a previously unknown class of molecules, unprotected aziridine aldehydes, has been identified. We highlight the application of these valuable intermediates by generating complex pentacyclic frameworks in one simple operation.

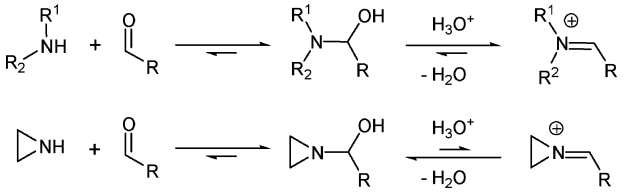
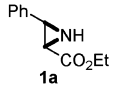
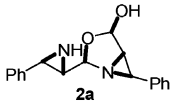
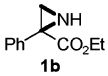
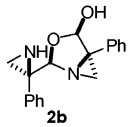
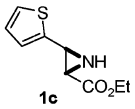
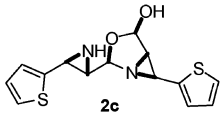
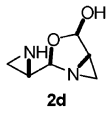
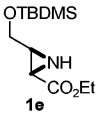
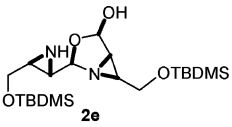


Figure 1. Effect of ring strain on reversible formation of iminium ions from secondary amines and aldehydes.

The aziridine aldehydes were prepared from aziridine esters,[7] which were in turn made from readily available epoxy esters by treatment with sodium azide followed by triphenylphosphine.[8] The reduction of the aziridine ester **1a** with DIBAL furnished a bench-stable white solid in 83% yield (Table 1, entry 1). Gratifyingly, its X-ray crystallographic analysis (Figure 2) revealed that the aziridine aldehyde was formed and had undergone a diastereoselective homodimerization, rather than giving products of premature condensation via iminium ion formation, confirming our hypothesis that the aziridine and aldehyde functionalities can coexist.

Several aziridine aldehydes with different substitution patterns were prepared using this method (Table 1). The products are off-white solids that can be purified by recrystallization with the exception of **2e** and the parent aziridine aldehyde **2d**, which is a water-soluble, colorless liquid. In order to establish the synthetic utility of aziridine aldehydes, we evaluated the nature of equilibrium between their dimer and monomer states (Scheme 1).

Table 1. Aziridine Aldehyde Dimers Obtained through DIBAL Reduction of Aziridine Esters[a]

entry	aziridine ester	product	yield[b]
1	 **1a**	 **2a**	83%
2	 **1b**	 **2b**	81%
3	 **1c**	 **2c**	92%
4	 **1d**	 **2d**	76%
5	 **1e**	 **2e**	94%

[a] Reactions were carried out using 1 equiv of ester and 2 equiv of DIBAL in toluene at −78 °C. [b] Isolated yields.

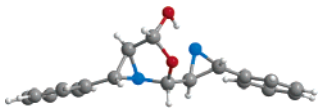
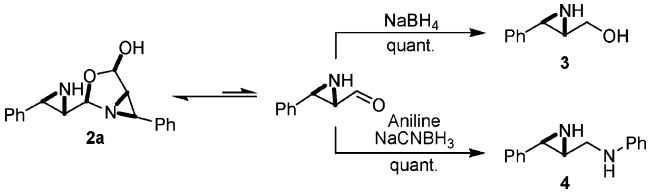


Figure 2. X-ray structure of aziridine aldehyde dimer **2a**.

Scheme 1. Equilibrium between Homodimer **2a** and Free Aziridine Aldehyde with Subsequent Reductive Transformations



The monomeric aldehydes can be obtained in MeOH/THF and can be cleanly reduced with sodium borohydride to give the aziridine alcohols (e.g., **3**). Furthermore, reductive amination of **2a** with aniline furnished the diamine **4** in quantitative yield. This result demonstrates that the aziridine functional group is orthogonal to the aldehyde *in the course of the reaction*, allowing selective reactivity with an external secondary amine at the aldehyde carbon.

Motivated by ongoing interest in efficient construction of complex alkaloid scaffolds[9] and encouraged by the chemoselective

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Scheme 2. Preparation of Pentacycles from Aziridine Aldehydes and *N*-Benzyl Tryptamine

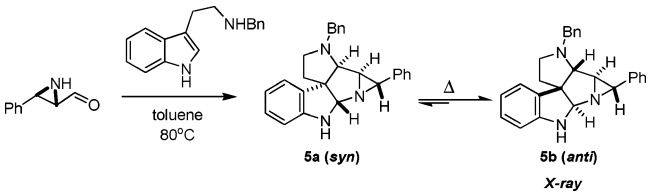
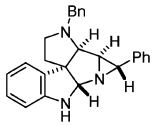
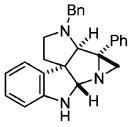
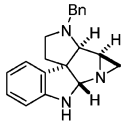
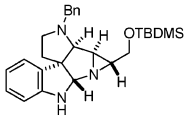


Table 2. Pentacycles Derived from Aziridine Aldehydes and *N*-Benzyl Tryptamine[a]

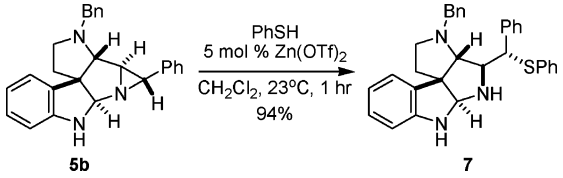
entry	dimer	T (°C)	time	pentacycle[b]	yield[c]	*syn*/*anti*[d]
1	**2a**	0	3 h		97% 94%	8:1 20:1[e]
2	**2b**	40[f]	8 h		81%	2:1
3	**2d**	0	3 h		74%	1.5:1
4	**2e**	0	3 h		94%	3:1

[a] Unless stated otherwise, the reactions were carried out using 1 mmol of the dimer (2 mmol of aldehyde) and 2 mmol of *N*-benzyl tryptamine in 2 mL of TFE at 0 °C for 3 h. [b] Major diastereoisomer shown. [c] Isolated yield. [d] Based on crude ^{1}H NMR. [e] Reaction was run at −20 °C. [f] Elevated temperature was required for reaction to occur.

iminium ion chemistry in the presence of an unprotected NH aziridine moiety (Scheme 1), we further probed the orthogonal relationship between the aziridine and aldehyde groups by reacting **2a** with *N*-benzyltryptamine (**6**), a bifunctional nucleophile capable of iminium ion formation.[10] When aziridine aldehyde **2a** was reacted with **6** in toluene at 80 °C for 16 h, a 2:1 diastereomeric mixture of pentacycles **5a** and **5b** was isolated in 74% yield as an off-yellow solid (Scheme 2 and Table 2). The diastereomeric structures were assigned using 2D-NMR and verified using X-ray analysis of **5b**. The aziridine ring of **5b** can be readily opened by benzenethiol in the presence of 5 mol % $Zn(OTf)_2$ resulting in a stable aminal product (Scheme 3). The reaction is completed within 1 h with >99% regioselectivity.

The diastereoselectivity of polycyclization was explored using a variety of protic and aprotic solvents. When **5a** was heated in toluene with a catalytic (5 mol %) amount of water, a 10:1 mixture of **5b** and **5a** was obtained. Since the thermodynamic product was accessible under thermal conditions, a diastereoselective route to **5a** was pursued. Polyfluorinated alcohols proved to be the optimal media. When **2a** and **6** were reacted in trifluoroethanol (TFE) at 0 °C for 3 h, selective formation of the pentacyclic adduct **5a** took place in 97% yield. Gratifyingly, when the reaction temperature was decreased to −20 °C, a >20:1 ratio of **5a**/**5b** was obtained. The heteroaromatic aziridine aldehyde **2c** exhibited poor reactivity as it was only moderately soluble in trifluoroethanol at room temperature. Importantly, the parent aziridine aldehyde **2d**, which along with **2e** is the most synthetically versatile compound of this series, gave high yield of the pentacyclic product.

Scheme 3. Regioselective Ring Opening of **5b** with Benzenethiol



In summary, an efficient synthesis of bench-stable amino aldehydes has been developed and their synthetic utility has been demonstrated. These novel molecules exist as dimers and contain two orthogonal reaction centers, namely an amine/aziridine and an aldehyde, over the span of only three atoms.[11] Their ability to act as linchpins has been evaluated in complex heterocycle synthesis. The *amphoteric* nature of aziridine aldehydes should facilitate invention of new transformations as well as efficient generation of complex molecular skeletons with minimal use of protecting group manipulations.

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Supporting Information Available: Compound characterization and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) (a) D-Glucosamine, a naturally occurring amino aldehyde, is stable as a cyclic aminal salt: Fischer, E.; Leuchs, H. *Ber. Dtsch. Chem. Ges.* **1902**, *36*, 24. (b) Glycinal was characterized through degradation studies: Fischer, E. *Ber*. **1908**, *41*, 956. Fischer, E. *Ber*. **1908**, *41*, 1019. (c) For a preparation of histidinal dihydrochloride, see Adams, E. *J. Biol. Chem.* **1955**, *217*, 317.

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(5) Ooi, T.; Saito, A.; Maruoka, J. *J. Am. Chem. Soc.* **2003**, *125*, 3220.

(6) Strained iminium ions derived from aziridines can be formed under forcing conditions. See Daly, J. *J. Org. Chem.* **1970**, *35*, 1861.

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(9) Hesse, M. *Alkaloids: Nature's Curse or Blessing?*; John Wiley & Sons: New York, 2002.

(10) For application of tryptamine derivatives in the Pictet−Spengler reaction, see Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

(11) We have observed no evidence for epimerization of the amino aldehyde α-stereocenter under basic or acidic conditions.

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