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Facile preparation of allyl amines and pyrazoles by hydrazinolysis of 2-ketoaziridines

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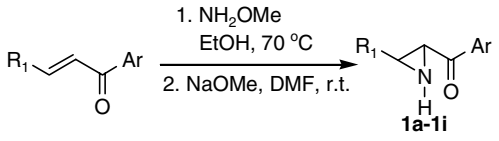
Abstract—Allyl amines and pyrazoles can be obtained by hydrazinolysis of 2-ketoaziridines. A variety of aziridines, including N-unprotected, N-substituted, as well as bicyclic enamine and aminal type, can be transformed into diversely substituted linear or cyclic products. The hydrazinolysis of homochiral aziridines proceeds without racemization.

Allyl amines are often found in the structures of natural products and pharmaceuticals. Specific examples of the allyl amine-containing drugs are flunarizine,[1] naftifine,[2] and terbinafine,[3] to name a few. In addition, allyl amines are useful synthetic intermediates for the preparation of other value-added molecules. One of the well known examples of allyl amine involvement in synthesis is the catalytic asymmetric hydrogen migration during the syntheses of (−)-menthol, α-tocopherol, and methoprene.[4] Traditional synthetic routes to allyl amines have been based on (a) Gabriel synthesis, (b) reaction between lithium amides and substituted alkynes in the presence of zirconocene complexes, (c) allylic amination catalyzed by the transition metal complexes, (d) azidation of allyl halides followed by azide reduction, (e) reduction of α,β-unsaturated imines or oximes, (f) reaction between nitrobenzenes and allylmagnesium halides followed by reduction, and (g) sigmatropic rearrangement of allyl ether derivatives.[5]

Our interest in synthetic applications of functionalized aziridines[6] has led us to investigate their use in the synthesis of other nitrogen-containing molecules such as allyl amines.[7] In the present study, 2-ketoaziridine starting materials were prepared using 1,4-addition of methoxyamine to α,β-unsaturated ketones followed by base-promoted ring closure (**1a**–**i**)[8] (Scheme 1), electrochemical olefin aziridination (**1l**),[6a] or by further derivatization of unprotected aziridines (**1k**,**m**,**n**).[9]



Scheme 1. Synthesis of 2-ketoaziridines.

When we applied the hydrazinolysis conditions to **1a**–**i**, the 2-alkylaziridines were transformed into the corresponding allyl amine derivatives and 3,5-disubstituted pyrazoles (Scheme 2).[10] The reaction proceeded equally well in ethylene glycol at 100 °C with potassium hydroxide as base or in *tert*-butanol at the same temperature with sodium methoxide as base. Product purification and isolation was facilitated using *tert*-butanol. The scope of base-mediated hydrazine reduction of 2-ketoaziridines was investigated (Table 1). The selectivity between allyl amine and pyrazole formation is moderate to high. The reactions are clean and the separation of pyrazoles from allyl amines can be easily performed on silica gel.[11,12]

The unsubstituted aziridines are within the scope of the process. The aziridines which contain sterically demanding R_1 substituents also afford good yields of allyl amines, indicating that the reaction is not sensitive to substitution at this position (Table 1, entries 1–2). Chalcone-derived aziridines (Table 1, entries 3–9) afford lower selectivity for allyl amine formation if the aryl group distal to the carbonyl functionality contains an electron-donating substituent or if the proximal aryl

Keywords: Allyl amine; Pyrazole; 2-Ketoaziridine; Hydrazinolysis.
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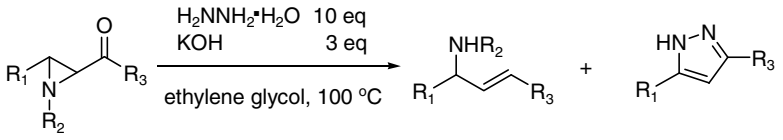


Scheme 2. Hydrazinolysis of 2-ketoaziridines.

Table 1. Hydrazine reduction of 2-ketoaziridines under alkaline conditions

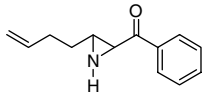
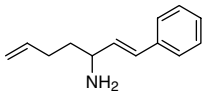
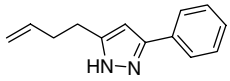
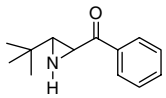
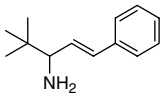
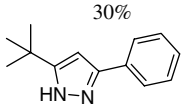
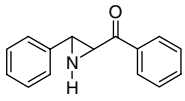
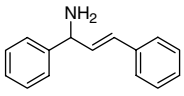
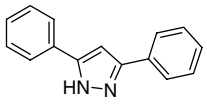
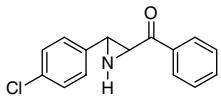
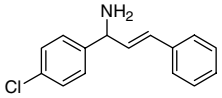
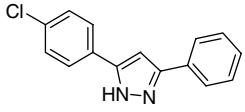
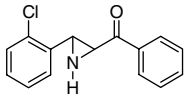
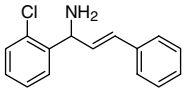
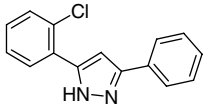
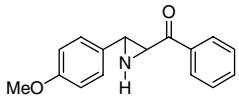
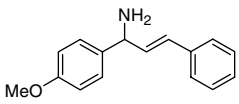
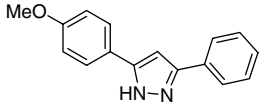
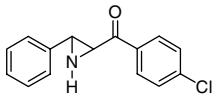
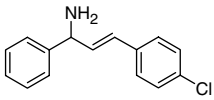
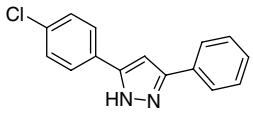
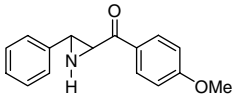
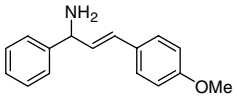
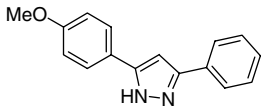
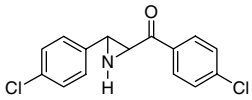
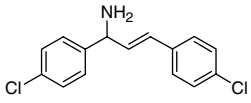
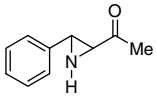
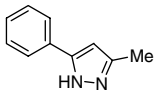
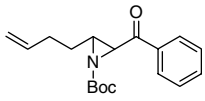
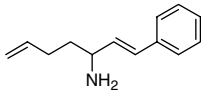
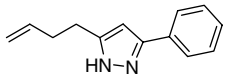
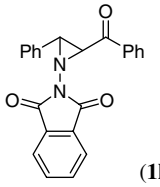
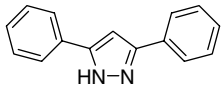
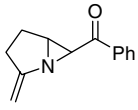
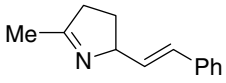
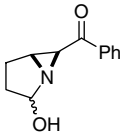
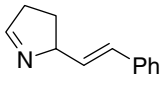
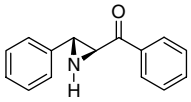
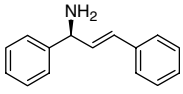
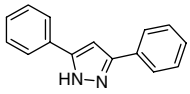
Entry	Starting material	Yield[a]	
		Amine product	Pyrazole product
1	 (**1a**)	 (**2a**) 60%	 (**3a**) 30%
2	 (**1b**)	 (**2b**) 67%[b]	 (**3b**) 22%
3	 (**1c**)	 (**2c**) 46%	 (**3c**) 14%
4	 (**1d**)	 (**2d**) 65%	 (**3d**) 23%
5	 (**1e**)	 (**2e**) 60%	 (**3e**) 14%
6	 (**1f**)	 (**2f**) 11%	 (**3f**) 8%
7	 (**1g**)	 (**2g**) 33%	 (**3e**) 18%

Table 1 (*continued*)

Entry	Starting material	Yield[a]	
		Amine product	Pyrazole product
8	 (**1h**)	 (**2h**) 69%	 (**3f**) 13%
9	 (**1i**)	 (**2i**) 62%	0%
10	 (**1j**)	0%	 (**3j**) 58%
11	 (**1k**)	 (**2a**) 50%	 (**3a**) 34%
12	 (**1l**)	0%	 (**3c**) 45%
13	 (**1m**)	 (**2m**) 65%[c]	0%
14	 (**1n**)	 (**2n**) 40%[d]	0%
15	 [(2*S*,3*R*)-**1c**] ee > 99%	 [(1*S*)-**2c**] 46%, > 99%ee[e]	 (**3c**) 14%

[a] Isolated yield.
[b] Based on 95% conversion.
[c] The initial enamine product was tautomerized to cyclic imine.
[d] Dehydrated product observed.
[e] Enantiomeric excess was determined by the Mosher acid method.

ring contains an electron-withdrawing substituent. Overall, the distal electron-withdrawing substituents and the proximal electron-donating substituents led to enhanced reactivity. These reactions result in moderate to good yields. However, if methyl ketone is used instead of phenyl ketone, none of the allyl amine is formed and the pyrazole is the only product observed (Table 1, entry 10). The activated aziridine which contains amide nitrogen also afford higher yield of pyrazole (Table 1, entry 11). *N*-Aminophthalimide containing aziridine does not result in any allyl amine formation (Table 1, entry 12). The strained bicyclic enamine gives clean formation of allyl amine which tautomerizes to imine under the reaction conditions (Table 1, entry 13). The compounds of this type can be readily and stereoselectively reduced to the corresponding pyrrolidine derivatives using DIBAL-H.[9] The aldehyde derived aziridine **1n** leads to cyclic imine **2n** after dehydration of the allyl amine product (entry 14). Finally, if one of the enantiomers of **1c** is used as the starting material, the reaction only affords corresponding homochiral allyl amine (Table 1, entry 15), indicating that the reaction process is stereospecific.

In a typical Wolff–Kishner reduction, the anionic portion of intermediate **B** is protonated followed by further deprotonation of the N=N–H fragment and subsequent elimination of nitrogen to give the methylene group. In the case of 2-ketoaziridines, intermediate **B** reacts with the adjacent aziridine ring at the alpha position and opens it up to give the allyl amine product (Fig. 1, path a). Alternatively, the anionic nitrogen center in intermediate **A** can attack the aziridine ring at the beta position to form the pyrazole ring (Fig. 1, path b). This result suggests that the phenyl substituent is necessary to stabilize the negative charge which later opens the aziridine ring in the process of allyl amine formation. Anion stabilizing substituents should facilitate allyl amine formation relative to pyrazole formation, which is reflected in entry 10.

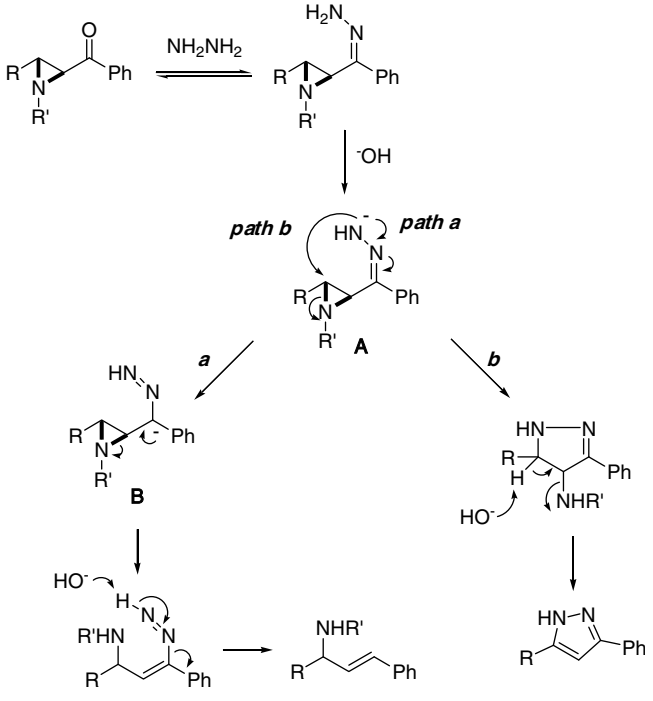


Figure 1. Base-mediated hydrazinolysis of 2-ketoaziridines.

In conclusion, simple hydrazinolysis of 2-ketoaziridines affords allyl amines in good yields and moderate selectivities. Electronic and steric effects from the substituents influence the reactivity of the substrates and selectivity between allyl amine and pyrazole product. In the cases of bicyclic aziridines, cyclic imines are the only products. Enantiomerically pure allyl amine can be synthesized if the homochiral aziridine is used as the starting material.

Acknowledgements

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Supplementary data

NMR spectra of compound **1a**–**n**, **2a**–**i**,**m**,**n**, **3a**–**f**, and **3j**. Text describing the general procedure for the preparation of **1b**–**1i**, procedure for preparation of **1k**,**n**, HPLC condition for separation of (2*S*,3*R*)-**1c** and procedure for ee determination of (1*S*)-**2c**. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.11.039.

References and notes

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2. Monk, J. P.; Brogden, R. N. *Drugs* **1991**, *42*, 659.
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12. Typical procedure for the synthesis of allyl amine. A mixture of (3-but-3-enyl-*trans*-aziridin-2-yl)-phenylmethanone (**1a**, 100 mg, 0.5 mmol), hydrazine monohydrate (250 mg, 5.0 mmol), potassium hydroxide (84 mg, 1.5 mmol), and ethylene glycol (2 mL) was stirred at 100 °C for 1 h. After no starting material detected by TLC, dichloromethane (10 mL), and water (10 mL) were added and separated. Water layer was extracted with another portion of dichloromethane (5 mL). The combined organic layers were washed with water (10 mL) followed by drying over magnesium sulfate. The solvent was removed in vacuum. The residue was purified on a silica gel column (hexane/ethyl acetate = 6/4, followed by methanol/dichloromethane/triethyl amine = 10/89/1), to afford 1-styrylpent-4-enylamine (**2a**) as colorless oil (56 mg, 60%) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25–7.37 (m, 5H), 6.50 (d, $J = 11.6$ Hz, 1H), 5.79–5.86 (m, 1H), 5.57 (dd, $J = 11.6$, 6.0 Hz, 1H), 4.94–5.04 (m, 1H), 3.89–3.91 (m, 1H), 2.11–2.17 (m, 2H), 1.58–1.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.3, 137.3, 129.1, 128.6, 128.3, 128.2, 126.9, 114.7, 48.2, 37.3, 30.4; HR-MS (EI) m/z: calcd for $C_{13}H_{16}N$ 186.1283, found 186.1278. 5-But-3-enyl-3-phenyl-1*H*-pyrazole (**3a**) (29 mg, 30%).^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75–7.77 (m, 2H), 7.40–7.44 (m, 1H), 7.30–7.36 (m, 2H), 6.42 (s, 1H), 5.84–05.94 (m, 1H), 5.04–5.14 (m, 2H), 2.79 (t, $J = 7.6$ Hz, 2H), 2.43–2.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.4, 128.7, 127.9, 125.7, 115.7, 101.2, 33.2, 25.9; HR-MS (EI) m/z: calcd for $C_{13}H_{14}N_2$ 198.1157, found 198.1154.