Facile preparation of α-amino ketones from oxidative ring-opening of aziridines by pyridine *N*-oxide†

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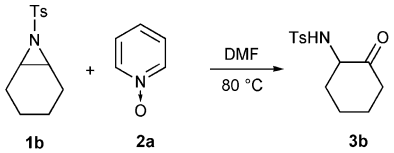
The oxidative ring-opening reaction of a variety of activated aziridines by pyridine *N*-oxide provided α-amino ketones or α-amino aldehydes in good yields.

Aziridine derivatives are versatile intermediates in organic synthesis because of their ability to function as carbon electrophiles.[1] Ring-opening reactions of aziridines with various heteroatom nucleophiles as well as some carbon nucleophiles have been well documented;[2] some other transformations of aziridines have also been reported.[3] In contrast, few reports have appeared in the literature on the direct conversion of aziridines to α-amino carbonyl derivatives,[4,5] even though they are an important subunit of biologically active natural products[6a] and are also useful intermediates in organic synthesis.[6b] Nozaki and Heine reported that the direct oxidative ring-opening of aziridines in DMSO gave α-amino ketones respectively.[4a,b] Recently, Rao and co-workers reported that the oxidative ring-opening of aziridines by IBX in the presence of β-CD, or by NBS combined with CAN, resulted in α-amino ketones.[4c,4e] During studies on the organophosphine-mediated transformation of aziridines and on extension of the reaction scope,[2a,7] we studied the conversion of aziridines to α-amino ketones. It was found that heating the aziridines in DMSO provided a simple synthesis of α-amino carbonyl derivatives;[4a,b] however, all reactions require DMSO as solvent. No product resulted when 1–10 eq. of DMSO was used in several common solvents, such as CH_2Cl_2, THF, MeCN, benzene, AcOEt and Et_2O, even when mixed solvents (MeCN or THF with DMSO in a 1 : 1 ratio) were used. Recognizing that DMSO is an oxide of a sulfide, we deduced that amine *N*-oxides should also play a similar role in this transformation. In this communication, we would like to report that the reaction of aziridines with a stoichiometric amount of pyridine *N*-oxide afforded α-amino carbonyl compounds in good to high yields.[8]

Reaction of aziridine **1b** with 1.2 eq. of pyridine *N*-oxide **2a** in DMF at 80 °C provided the desired α-amino ketone in 60% yield (eqn (1)). Screening of solvents showed that the reaction in toluene gave **3b** in 76% yield, while that in other solvents, such as CH_2Cl_2, CH_3CN, THF and ^{i}PrOH, gave a lower yield. Increasing the amount of pyridine *N*-oxide to 2–3 eq. did not improve the yield of product.

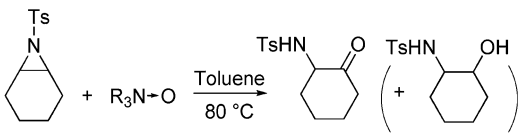


1b **2a** **3b** (1)

Different amine oxides were also tested (Table 1). This showed that the presence of an electron-donating group on the pyridine ring improved the reaction rate, but not the yield (entry 2), and that an electron-withdrawing group on the pyridine ring resulted in very little product after 40 h (entry 3). Both quinoline and 3-methylpyridine *N*-oxides gave moderate yields, but collidine *N*-oxide delivered a lower yield of product (entries 4 and 6 *vs.* entry 5) for steric reasons. Aliphatic amine oxides provided lower yields of α-amino ketones as well as the undesired α-amino alcohols **4** in moderate yields (entries 7 and 8).

Using pyridine *N*-oxide in toluene, various aziridines were tested, and the results are shown in Table 2. Both Ts and PhCO substituents at the aziridine nitrogen give the desired product (entry 4). The reaction of symmetrically disubstituted *meso*-aziridines **1a** and **1b** afforded the corresponding α-amino ketones in good yields (entries 1 and 2), while aziridine **1c** (derived from cycloheptene) gave only a trace of product (entry 3). Both aziridines **1e** (derived from styrene) and **1f** (derived from indene) gave only products resulting from benzylic attack (entries 5 and 6). For aziridine **1i**, reaction gave more of the benzyl-attacked product **3i** (entry 9), but for a disubstituted aziridine derived

Table 1 Oxidative ring opening of aziridine **1b** with different amine oxides[a]



1b **2** **3b** **4**

Entry	Amine *N*-oxide **2**	Time/h	Yield of **3b** (%)
1	Pyridine *N*-oxide	24	76
2	4-Methoxypyridine *N*-oxide	5	75
3	4-Acetylpyridine *N*-oxide	40	Trace
4	3-Methylpyridine *N*-oxide	15	62
5	Collidine *N*-oxide	24	41
6	Quinoline *N*-oxide	15	60
7	Me_3N *N*-oxide	4	22[b]
8	*N*-Morpholine *N*-oxide	5	14[b]

[a] Run at 80 °C in toluene using 1.2 eq. of amine oxide. [b] 60% yield of product **4** was also separated.

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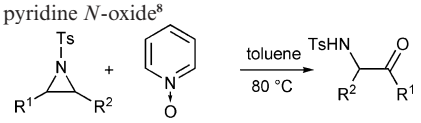
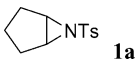
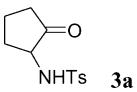
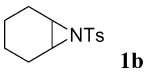
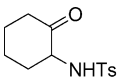
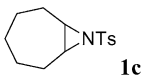
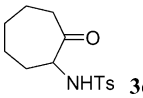
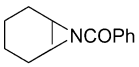
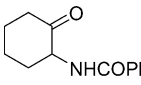
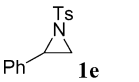
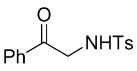
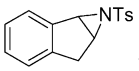
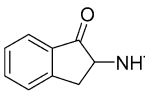
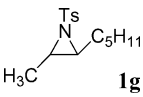
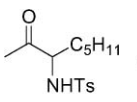
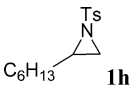
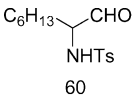
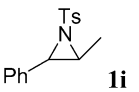
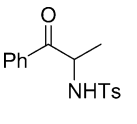
Table 2 Oxidative ring-opening of aziridines using pyridine *N*-oxide[8]



1 2a 3

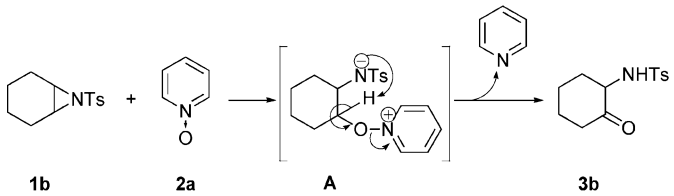
Entry	Aziridine	Time/h	Product	Isolated yield (%)
1	 **1a**	24	 **3a**	77
2	 **1b**	48	 **3b**	76
3	 **1c**	64	 **3c**	Trace
4	 **1d**	12	 **3d**	80
5	 **1e**	10	 **3e**	40
6	 **1f**	10	 **3f**	55
7[a]	 **1g**	20	 61 : 39 **3g** **3g′**	74
8[a]	 **1h**	24	 60 : 40 **3h** **3h′**	20
9[a]	 **1i**	24	 81 : 19 **3i** **3i′**	82

[a] Ratio of products was determined by ^{1}H NMR spectroscopy.

from an aliphatic alkene, **1g**, the regioselectivity of reaction was low (entry 7). Overall, reactions of disubstituted aziridines provided the corresponding carbonyl products in satisfactory yield (entries 1, 2, 4, 6, 7, and 9), but those of monosubstituted aziridines gave lower yields accompanied by some unidentified byproducts (entries 5 and 8).

The conversion of benzyl bromides to benzaldehydes in the presence of amine oxides is well-documented reaction.[9] The oxidative ring-opening reaction of aziridine with pyridine *N*-oxide may proceed in a similar way: nucleophilic attack of amine oxide to the aziridine gives rise to the intermediate **A**, proton-transfer and elimination of pyridine then affording α-amino ketones (Scheme 1).[9]

In summary, pyridine *N*-oxide was found to be an efficient reagent for oxidative ring-opening of activated aziridines, providing good yields of α-amino carbonyl compounds. Further investigations on the asymmetric version and extension of the reaction are in progress.



Scheme 1 Possible mechanism of oxidative ring-opening reaction of aziridine with amine oxide.

Acknowledgements

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Notes and references

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8 Typical procedure for the oxidative ring opening of aziridines by pyridine *N*-oxide: An oven-dried tube was charged with **1b** (126 mg, 0.5 mmol), pyridine *N*-oxide (57 mg, 0.6 mmol) and toluene (2 mL) under Ar, the mixture warmed to 80 °C and stirred at this temperature until the starting material **1b** disappeared (monitored by TLC). The solvent was removed under reduced pressure and the residue was purified by chromatography (silica gel: petroleum ether–AcOEt = 3 : 1) to afford **3b** as a white solid (102 mg, 76% yield), mp 116–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$/TMS) (ppm): δ = 1.50–1.66 (m, 3H), 1.82–1.85 (m, 1H), 2.03–2.09 (m, 1H), 2.21–2.25 (m, 1H), 2.40 (s, 3H), 2.44–2.55 (m, 2H), 3.74 (m, 1H), 5.78 (d, J = 4.5 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$/TMS) (ppm): δ = 21.4 (Ar-CH_3), 23.8 (CH_2), 27.3 (CH_2), 36.7 (CH_2), 40.7 (CH_2), 60.5 (NCH), 126.9 (Ar-C), 129.6 (Ar-C), 136.8 (Ar-C), 143.5 (Ar-C), 205.7 (C=O) EI-MS m/z (intensity): 267 (10) [M^+], 91 (100) [p-$MeC_6H_4^+$]. IR (cm^{-1}): 1708 (s, C=O), 3276 (s, NH).

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