Reduction of 2-Acylaziridines by Samarium(II) Iodide. An Efficient and Regioselective Route to β-Amino Ketones and Esters

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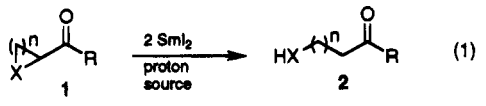
Samarium(II) iodide (SmI_2) is a powerful, one-electron reducing agent, capable of reducing a wide range of functional groups with a high degree of selectivity.[1] One of the most widely applied processes using SmI_2 involves the reductive cleavage of α-heterosubstituted carbonyl substrates.[1] Substrates possessing small rings adjacent to a carbonyl group comprise an important subgroup of compounds that can be reductively cleaved. Epoxy ketones[2] and esters,[3] vinyl epoxides,[4] and cyclopropyl ketones[5] have been reduced with SmI_2 to provide the corresponding ring-opened products (eq 1). α-Keto tet-



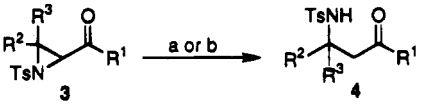
X=O n=1,4 R=alkyl, aryl, O-alkyl

X=CH_2 n=1 R=alkyl

rahydropyrans have also been reduced to afford the ring-opened hydroxy ketones in high yield, indicating that this type of reduction is not limited to small ring compounds.[6]

Noticeably absent from this list of substrates are those containing nitrogen heterocycles. To fill this void, a study was undertaken to determine if nitrogen substituents could serve as adequate leaving groups in the reductive cleavage process. At the outset, the reductive cleavage of aziridines, activated by an adjacent carbonyl group, was selected for this investigation. This ring scission would provide a novel method for the preparation of β-amino carbonyl compounds[7] which are useful building blocks for the synthesis of biologically active compounds. This mode of reductive cleavage has been observed in certain instances upon treatment of activated aziridines with various cuprate reagents.[8] Additionally, chromium(II) chloride has been employed for the reductive cleavage of a 2-acylaziridine in a formal synthesis of perhydrohistrionicotoxin.[9] The use of SmI_2 for this purpose offers advantages over these methods and would be an attractive method for the synthesis of synthetically useful β-amino carbonyl compounds. Herein, preliminary results are presented outlining the feasibility and generality of this reductive cleavage.

Table 1. Reduction of 2-Acylaziridines with SmI_2



aziridine	product (% yield)
3a R^1 = Me, R^3 = Ph	**4a** (87)[a]
3b R^1 = Me	**4b** (95)[b]
3c R^1 = Me, R^2, R^3 = Me	**4c** (78)[b]
3d R^1, R^2 = $(CH_2)_3$	**4d** (87)[b]

[a] 2.5 equiv of SmI_2, MeOH, THF, −90 °C. [b] 2.5 equiv of SmI_2, MeOH, THF, 0 °C.

Initially, a series of 2-acyl-*N*-tosylaziridines was prepared for study. These were readily available from the $Cu(acac)_2$- or $Cu(CH_3CN)_4ClO_4$-catalyzed aziridination of α,β-unsaturated ketones using (*N*-(*p*-toluenesulfonyl)-imino)phenyliodinane (PhI=NTs).[10] Treatment of **3a** with 2.5 equiv of SmI_2 in THF–MeOH solvent at −90 °C[2] provided the β-*N*-tosylamino ketone in high yield, as shown in Table 1.[11] The reduction was extremely rapid. Thin layer chromatographic analysis indicated the complete consumption of the aziridine immediately after addition of the SmI_2. In the course of optimization experiments, no decrease in the yield of the reactions was observed when they were performed at higher temperatures, although a substantial exotherm was noted when the reactions were carried out at room temperature. For convenience, the remaining reductions were performed at 0 °C. As shown in Table 1, these β-(*N*-tosylamino) ketones were obtained in excellent yields with no sign of any desulfonylation.[12]

Next, the efficacy of this reductive cleavage with *N*-tosylaziridine-2-carboxylates was examined.[10] At the outset, treatment of aziridine **5a** with 2.5 equiv of SmI_2 in THF–EtOH solvent at 0 °C provided a mixture of α- and β-amino esters. The reduction of esters by electron transfer agents is more difficult than that of ketones. In the present case, it appears that Sm(III) Lewis acid-

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(11) General procedure for the reduction of 2-acylaziridines with SmI_2: To a suspension of Sm powder (451 mg, 3.0 mmol) in THF (6.0 mL) at room temperature was added diiodomethane (669.7 mg, 2.5 mmol). The resultant olive-green slurry was stirred at ambient temperature for 2 h, after which time the resulting dark blue slurry of SmI_2 was cooled to 0 °C (ice/water) and treated with the aziridine (1 mmol) in MeOH (1 mL) and THF (2 mL). The reaction mixture was stirred for 5 min at 0 °C, quenched at this temperature by the addition of saturated aqueous sodium bicarbonate, and then warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL), and the combined extracts were dried with anhydrous magnesium sulfate.
(12) SmI_2/DMPU in THF heated at reflux has been reported to be effective for the desulfonylation of *N*-sulfonylated amines. Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602.
(13) General procedure for the reduction of aziridine-2-carboxylate esters with SmI_2: To a suspension of Sm powder (451 mg, 3.0 mmol) in THF (6.0 mL) at room temperature was added diiodomethane (669.7 mg, 2.50 mmol). The resultant olive-green slurry was stirred at ambient temperature for 2 h, after which time the resulting dark blue slurry of SmI_2 was cooled to 0 °C (ice/water) and treated with a mixture of the aziridine (1 mmol) and *N*,*N*-dimethylethanolamine (445.7 mg, 5.0 mmol) in THF (2 mL). The reaction mixture was stirred for 5 min at 0 °C, quenched at this temperature by the addition of saturated aqueous sodium bicarbonate (2 mL), and then warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 or ethyl acetate (5 × 10 mL), and the combined extracts were dried with anhydrous magnesium sulfate.

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Scheme 1

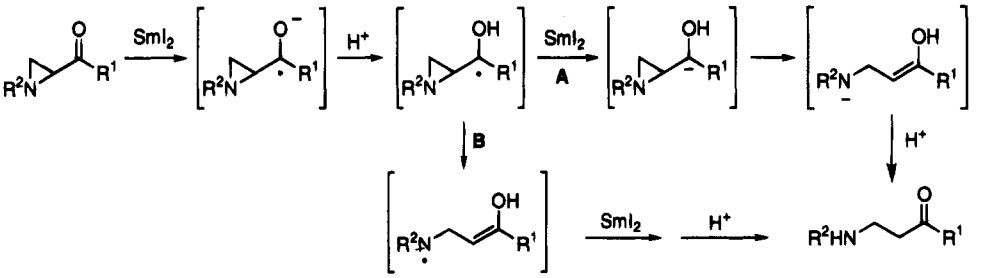
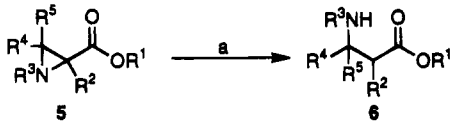


Table 2. Reduction of Aziridine-2-carboxylates with SmI_2



5 6

aziridine	product (% yield)
5a R^1 = Et, R^3 = Ts, R^5 = Ph	**6a** (87)
5b R^1 = Et, R^3 = Ts	**6b** (98)
5c R^1 = Et, R^3 = Ac, R^5 = Ph	**6c** (89)
5d R^1 = Et, R^3 = Boc, R^5 = Ph	**6d** (82)
5e R^1 = Me, R^3 = CO_2Et, R^2, R^4 = $(CH_2)_4$	**6e** (69)[b]
5f R^1 = Me, R^3 = Tr	**6f** (82)

[a] 2.5 equiv of SmI_2, 5.0 equiv of DMEA, THF, 0 °C. [b] 2.5:1 trans:cis.

promoted ring opening of the aziridine carboxylates is competing with the reductive mode of ring cleavage, thus leading to poor regioselectivity. However, as was the case for epoxy esters,[3] the use of 5.0 equiv of *N,N*-dimethylethanolamine (DMEA), in place of methanol or ethanol, provided exclusively the desired β-amino esters in excellent yields (Table 2).[13] The *N,N*-dimethylethanolamine is believed to serve several roles in these reductions. Not only does it act as an effective proton source, but it is also an efficient chelator of the Lewis acidic Sm(III) species in the reaction mixture. Furthermore, it may increase the reduction potential of the Sm(II) reductant. Through these effects, *N,N*-dimethylethanolamine prevents the regioselectivity problem observed in its absence.

To establish the generality of this method, the compatibility of this reductive cleavage with other nitrogen protecting groups was examined. To this end, several N–H aziridines were prepared from the corresponding epoxides using known methods.[14] With these aziridines in hand, a variety of common nitrogen protecting groups was introduced in a straightforward manner. Treatment of these substrates with 2.5 equiv of SmI_2 and 5.0 equiv of DMEA in THF at 0 °C provided the β-amino esters in good to excellent yields (Table 2). Reduction of substrate **5e** demonstrates an inherent limitation to this reductive cleavage, in that stereochemistry α to the carbonyl cannot be reliably controlled. Thus, a 2.5:1 mixture of diastereomers was obtained after aqueous workup in this case. The successful reductive cleavage of **5f** demonstrates that an electron-withdrawing group on nitrogen is not required for the ring scission.

A mechanistic rationale for the process is displayed in Scheme 1. Reaction of SmI_2 with the ketone carbonyl generates a ketyl, which is rapidly protonated by methanol. At this stage cleavage of the nitrogen heterocycle could occur by two distinct pathways. The protonated ketyl could undergo further reduction by the second equivalent of SmI_2, producing a carbanion. This anion would then induce the ring-opening of the aziridine (pathway A). Tautomerization of the intermediate enol would provide the observed β-amino ketone, with loss of stereochemistry adjacent to the carbonyl. Alternatively, the protonated ketyl could undergo a radical ring scission, producing the nitrogen radical (pathway B). Further reduction of the nitrogen radical to the nitrogen anion by the second equivalent of SmI_2 followed by protonation would lead to the observed product.

In summary, a convenient method for the reduction of 2-acylaziridines and aziridine-2-carboxylates has been developed. The reduction of all of the substrates examined was extremely rapid and highly regioselective, giving rise to β-amino carbonyl compounds. This method appears to be general for both of the classes of aziridines mentioned above, and it also tolerates a variety of nitrogen protecting groups. This transformation should be highly useful in organic synthesis, and further development and extensions of the method are currently being explored.

Acknowledgment. This work was carried out with generous support from the National Institutes of Health.

Supporting Information Available: Spectral data for the aziridine substrates utilized in the reductive cleavage reactions. Procedures for the SmI_2-promoted reductions, and spectral data for the resulting β-amino ketones and esters (7 pages).

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