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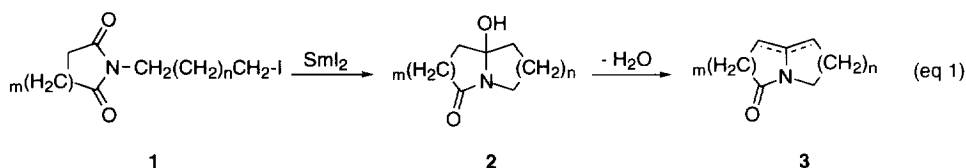
Reductive Cyclization of *N*-Iodoalkyl Cyclic Imides to Nitrogen-Fused Polycyclic Amides Induced by Samarium Diiodide

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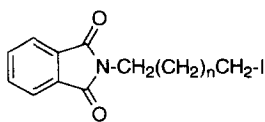
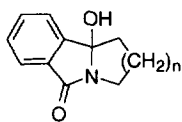
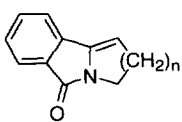
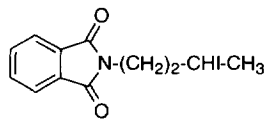
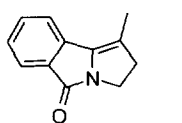
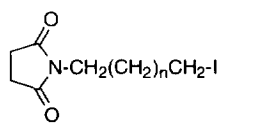
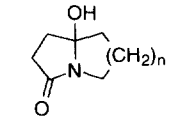
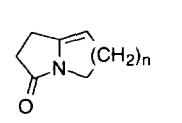
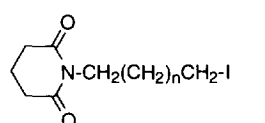
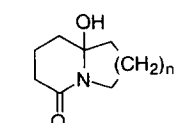
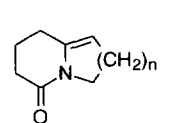
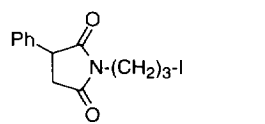
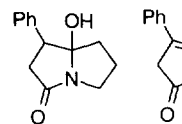
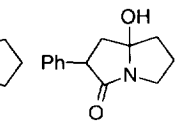
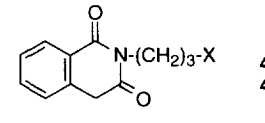


Abstract: SmI₂-promoted cyclizations of cyclic imides having 3-iodopropyl or 4-iodobutyl groups on the imide nitrogen have been studied for construction of nitrogen-fused polycyclic amides.
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Since the initial reports by Kagan regarding samarium diiodide, it has been extensively used in organic synthesis.¹ For example, this homogeneous reagent has been used to reduce aldehydes and ketones to ketyl radicals designed to undergo elimination² or cyclization reactions.³ In addition, samarium diiodide has been used to mediate Barbier-type coupling between alkyl halides and ketones intra- and intermolecular modes.⁴ More recent studies about intramolecular acyl substitution reactions of halo-substituted esters and lactones further proved the efficacy of these SmI₂-promoted reactions.⁵ Although a variety of functional groups have been used in SmI₂-promoted cyclization and substitution reactions, *N*-(haloalkyl)imides have not yet been reported. We felt that cyclizations of such substrates would provide nitrogen-fused polycyclic structures appropriate for the synthesis of alkaloid natural products.⁶ We report here our preliminary results on SmI₂-promoted cyclization of *N*-(iodoalkyl)-substituted cyclic imides of type **1** to construct pyrrolizidinone, indolizidinone, and quinolizidinone ring systems of type **2** and **3** (eq 1).



N-(Iodoalkyl)imide cyclization substrates were prepared by alkylation of corresponding imides with the appropriate dibromoalkane followed by a bromide-iodide exchange reaction.⁷ Phthalimides **4a**, **4b** and **4c** were subjected to 3 equivalents of SmI₂ in the presence of Fe(DBM)₃ catalyst to afford the results shown in Table 1.⁵ Imide **4a** cyclized smoothly at 0°C in 2-3 h to give a mixture of alcohol **5a** and dehydration product **6a**. Alcohol **5a** slowly dehydrated to **6a** during chromatographic separation. Thus, it was most convenient to heat the crude mixture of products with powdered 4 Å molecular sieves and catalytic amounts of *p*-TsOH in dichloromethane. In this manner, enamide **6a** was obtained in 95% yield from **4a**. In a similar manner, cyclization of **4b** was followed by spontaneous dehydration to provide **6b** in 94% yield. Secondary iodide **4c** gave **6c**, however, in only 43% yield. Succinimide and glutarimide derivatives also provided bicyclic amides.

Table 1. Reaction of *N*-(Iodoalkyl) Cyclic Imide with SmI_2

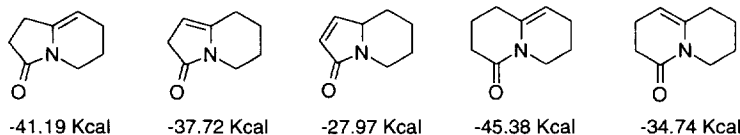
Substrate	Cyclization Products ^a (% Yield) ^{b, c}	
 4a : $n=1$ 4b : $n=2$	 5a : $n=1$ 5b : $n=2$	 6a : $n=1$ (95) 6b : $n=2$ (94)
 4c		 6c (43)
 4d : $n=1$ 4e : $n=2$	 5d+6d : $n=1$ (32) ^d 5e : $n=2$	 6e : $n=2$ (56)
 4f : $n=1$ 4g : $n=2$	 5f+6f : $n=1$ (35) ^d 5g : $n=2$	 6g : $n=2$ (60)
 4h	 5h (22)	 6h (37)
 4i : X=I 4j : X=H (44)	 5i (16) ^e	 6i (16) ^e

^a All products were characterized by their $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, IR and mass spectra. ^b 3 equiv. of SmI_2 , 0.03 equiv. of $\text{Fe}(\text{DBM})_3$, THF, 0 °C, 3 h. ^c Isolated yield after complete consumption of the starting imide. ^d Isolated as a mixture. ^e A diastereomeric mixture.

The extent and regiochemistry of dehydration depended on the size of the ring formed and the nature of substituents. Thus, *N*-(3-iodopropyl)succinimide (**4d**) cyclized to give a mixture of carbinol **5d** and enamide **6d** in 32% yield.⁸ Glutarimide derivative **4f** similarly gave a mixture of carbinol **5f** and enamide **6f** in 35% yield. Cyclization of **4e** and **4g**, however, led directly to six-membered ring enamides **6e** (56%) and **6g** (60%) after silica gel

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7. The N-iodoalkylimides were obtained by halide exchange reaction of the corresponding bromides (NaI, acetone, rt). N-Bromoalkylation of the imides was performed with 2-3 equivalents of the appropriate dibromoalkane, excess K₂CO₃, and 0.2 equivalents of *n*-Bu₄NBr in acetone at rt for 24 h. New, J. S.; Christopher, W. L.; Yevich, J. P.; Butler, R.; Schlemmer, Jr., R. F.; VanderMaelen, C. P.; Cipollina, J. A. *J. Med. Chem.* **1989**, *32*, 1147-1156.
8. Chromatographic separation of **5d** and **6d** was not possible and the mixture was still obtained after dehydration with *p*-TsOH and 4 Å molecular sieves in dichloromethane. For isolation of **5d**, known as pyrrolam C, from culture broth of *Streptomyces olivaceus* and structural determination, see: Grote, R.; Zeeck, A.; Stümpfel, J.; Zähler, H. *Liebig's Ann. Chem.* **1990**, 525-530.
9. The assignments of double bond position in **6e** and **6g** were made by ¹H-COSY experiments. Also, the relative stabilities of **6e**, **6g** and their regioisomers were estimated using MOPAC PM3 semiempirical calculations. These results suggest that thermodynamics control dehydration regiochemistry.



10. Treatment of **4e** or **4g** with activated magnesium turnings in THF heated at reflux failed to give any cyclized product.
11. Preparation of **6g**: To a solution of SmI₂ (6 mmol) in 30 mL of THF cooled at 0°C under argon atmosphere was added 43 mg (0.06 mmol) of Fe(DBM)₃ in 5 mL of THF via cannula followed by stirring for 10 min at 0°C. A solution of the imide **4g** (0.59g, 2 mmol) in 5 mL of THF was added via cannula and the resulting mixture was stirred for 3h at 0°C. The mixture was added to 50 mL of sat. NaHCO₃ solution and extracted three times with 50-mL portions of EtOAc. After drying (MgSO₄), the solvents were evaporated and the residue was chromatographed (SiO₂; EtOAc/hexane) to give 0.18g (60%) of **6g**. *R_f* = 0.53 (EtOAc:hexane = 3:1); IR (CH₂Cl₂, cm⁻¹) 1637; ¹H NMR (500 MHz, CDCl₃) δ 1.77 (m, 4H), 2.04 (m, 2H), 2.16-2.39 (m, 2H), 2.50 (t, *J* = 6.5 Hz, 2H), 3.73 (quint, *J* = 2.5 Hz, 2H), 4.71 (t, *J* = 3.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 19.1, 21.3, 21.9, 29.6, 32.9, 40.0, 103.7, 135.6, 168.8; MS *m/z* (%) 151 (M⁺, 90), 136(33), 122(58), 108(47), 95(100), 80(22), 67(25), 55(75).
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