BULLETIN
OF THE
KOREAN CHEMICAL SOCIETY

VOLUME 18, NUMBER 10
OCTOBER 20, 1997

BKCS 18(10) 1039-1132
ISSN 0253-2964

Communications

Mechanistic Studies on the Samarium Diiodide-Promoted Cyclization of N-Iodoalkyl Cyclic Imides

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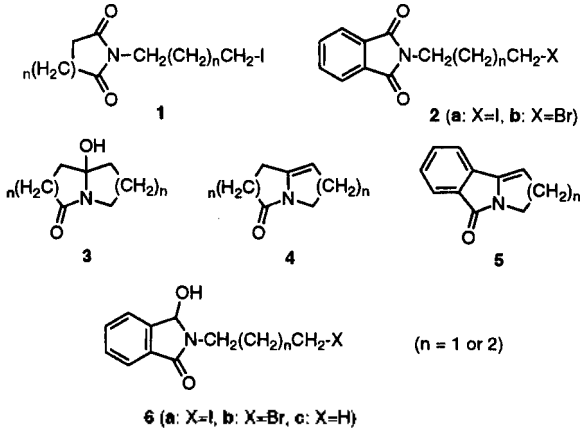
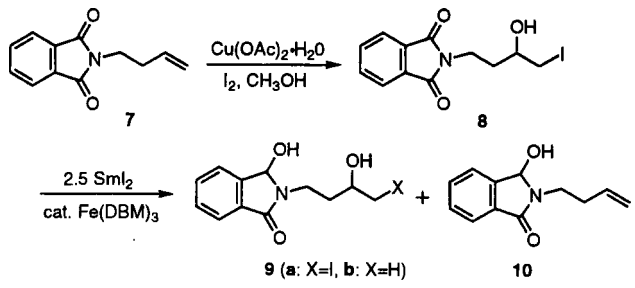
Received April 22, 1997

Pyrrolizidine, indolizidine and quinolizidine alkaloids have long been the attractive targets of many synthetic efforts due to their diverse and potent biological activities including antiviral, antitumor and glucosidase inhibitions.[1] In an effort to develope an expedient route to these nitrogen-fused bicyclic ring structures, we have studied a reductive cyclization of imides having ω-iodoalkyl groups on imide nitrogen using samarium diiodide as a strong and homogeneous reducing agent.[2] Thus, cyclic imides **1** and **2** were treated with samarium diiodide to give the corresponding polycyclic amides **3**, **4** and **5** in moderate to excellent yields.



Inter- and intramolecular Barbier-type coupling reactions between aldehydes or ketones with alkyl halides promoted by samarium diiodide are synthetically very useful methods.[3] Though recently studied intramolecular acyl transfer of haloesters is an apparent nucleophilic addition of Sm(III) carbanion to the ester carbonyl,[4] mechanistic details of the above mentioned Barbier-type couplings are not clearly defined among possibilities between carbanionic addition, ketyl-radical coupling, and Sm(III)-activated carbonyl-radical addition.[5] Reports from several research groups reveal the presence of alkylsamarium species in the intramolecular Barbier-type reactions, but there is also an evidence that single-electron transfer is involved before the cyclization. For example, a 5-iodoketone having 4-methoxy group successfully cyclized by samarium diiodide without the expected elimination reaction.[5a] This result indicates the presence of alkyl radical intermediate, not samariun carbanion, which adds to the ketone carbonyl possibly activated by Sm(III) species.

In our previous report on the SmI_2-promoted cyclization of *N*-(iodoalkyl) cyclic imides, we conducted a few reactions to get some mechanistic knowledge about this reductive cyclization process.[2] The cyclic imides **1** and **2a** were treated with less than stoichiometrical amounts of SmI_2 and the reaction products were isolated. While succinimides and glutarimides **1** (n=1, 2) provided cyclized products **3** and **4** with reduced yields, phthalimides **2a** gave mainly partially reduced products **6a** and small amounts of cyclization products **5**. Partial reduction only at the imide carbonyl was not observed with **1**. These results suggest that SmI_2-promoted cyclizations of imides may follow different pathways depending on the structure of imide. In the case of phthalimide **2a**, imide carbonyl was reduced first to the ketyl radical which, with no more reducing agent available, abstracted hydrogen from the reaction medium to give **6a**.[6] But, for the cyclization process, it is not clear whether it is ketyl radical-alkyl radical coupling, as we originally claimed, or ketyl ra-

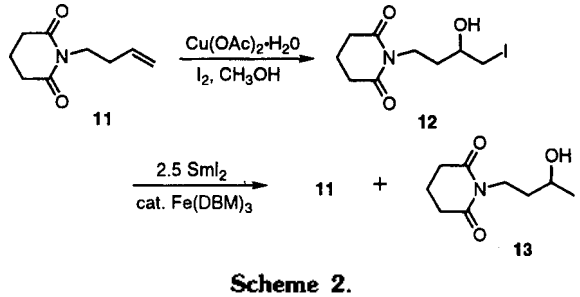


Scheme 1.

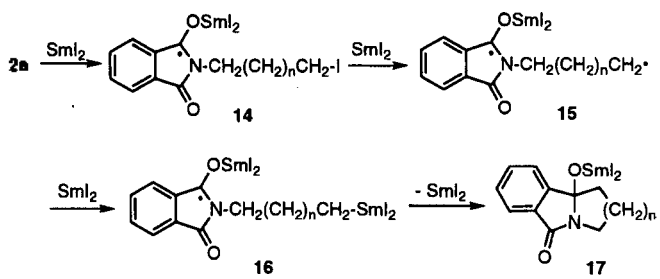
dical-carbanion coupling. For succinimide and glutarimide derivatives, the iodide seems reduced first since the imide carbonyl is more difficult to form ketyl radical than phthalimide carbonyl.[7] But we need more information to distinguish between simple carbanionic cyclization process and more complex ketyl formation, internal electron transfer to iodide followed by Sm(III)-activated radical-carbonyl addition process.

Better understanding of the mechanistic pathway of this reductive cyclization will help us in designing cyclic imides having appropriate substituents for the synthesis of polyhydroxylated nitrogen-fused bicyclic alkaloids. Thus, we prepared the following two imides and subjected to our usual cyclization condition. The imides **7** and **11** were prepared from the imides and 3-buten1-ol under Mitsunobu condition, and converted to iodohydrins **8** and **12**.[8] Internal participation of imide carbonyl oxygen to the iodonium intermediate provided the iodohydrins instead of methoxy analogs. When iodohydrin 8 was treated with 2.5 equivalents of SmI_2 and catalytic amounts of $Fe(DBM)_3$ in THF at 0 °C for 4h, reduction products **9a**, **9b** and elimination product **10** were formed in 38%, 23%, and 30% yields, respectively, without formation of any cyclized product (Scheme 1). When glutarimide **12** was subjected under the same condition, elimination product **11** (62%) and dehalogenated product **13** (10%) were formed (Scheme 2). Reduction at the imide carbonyl was not observed in this case. Partially reduced **9a** indicates the initial formation of a ketyl radical which was further reduced to give **9b** and **10**. Since alkyl radical having vicinal hydroxy group does not give the elimination product, it is highly probable that ketyl radical-Sm carbanion intermediate is involved in the reduction process. This result also eliminates the disputed possibility of single-electron transfer followed by Sm(III)-activated radical cyclization pathway.[9] Reductive eliminations of **12** to **11** and **13** also support the presence of samarium carbanionic intermediate.

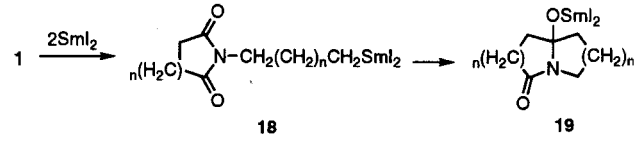
With the experimental result as above, we propose most



Scheme 2.



Scheme 3.



Scheme 4.

probable mechanistic pathway for SmI_2-promoted reductive cyclization of N-(ω-iodoalkyl) cyclic imides. The first equivalent SmI_2 reduces phthalimide **2a** to a quite stable ketyl radical **14** which is again reduced to a diradical **15** by the second equivalent of SmI_2. Instead of radical-radical coupling, this diradical is further reduced to radical-carbanion **16** which cyclized to **17** and regenerates one equivalent of SmI_2 (Scheme 3). Though it is risky to propose a new mechanism for the SmI_2-related reactions where we still have a limited amount of knowledge, and require more experimental evidences and further scrutiny, this proposed mechanism explains our experimental results better than generally considered radical-radical coupling or carbanionic addition process. Succinimide and glutarimide analogs are reduced first at the alkyl halide moieties by two-electron transfer and the resulting samarium carbanion **18** adds to the imide carbonyl to form the cyclization product **19** (Scheme 4). This process shows an identical mechanism to the nucleophlic acyl transfer reaction of haloesters.

In conclusion, we found that cyclic imides with ω-iodoalkyl group on nitrogen follow different mechanistic pathways depending on the structure of imide in their SmI_2-promoted reductive cyclizations. With the analysis of reduction products of iodohydrin-substituted imides, we propose a new mechanism that ketyl radical and samarium carbanion are involved in the cyclization of phthaimide derivatives while succinimides and glutarimides are following carbanionic addition to the imide carbonyl.

Acknowledgments. This research was financially supported by the Basic Science Research Institute Program (BSRI-96-3406) and the Organic Chemistry Research Center-KOSEF.

References

1. (a) Robins, D. J. *Nat. Prod. Rep.* **1995**, *12*, 413. (b) Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 535. (c) Liddell, J. R. *Nat. Prod. Rep.* **1996**, *13*, 187.
2. Ha, D.-C.; Yun, C.-S.; Yu, E. *Tetrahedron Lett.* **1996**, *37*, 2577.
3. (a) Molander, G. A. In *Comprehensive Organic Synthesis*;

Trost, B. M., Ed.; Pergamon: London, 1991; Vol. 1, pp 251-282. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Imamoto, T. In *Lanthanides in Organic Synthsis*; Academic Press: London, 1994; Chapter 4, pp 21-65.
4. (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216. (b) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705. (c) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1996**, *118*, 4059. (d) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37*, *suppl. 1*, 175.
5. (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112. (b) Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050. (c) Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1992**, *57*, 793. (d) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett.* **1992**, 943.
6. (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872.
7. To compare the relative reduction potentials of the imide carbonyls, **1** and **2** were reacted with Zn/AcOH in ether at room temperature. Phthalimide **2a** was reduce to give **6c**, and partially reduced **6b** was obtained from **2b**. Under the same condition, succinimide and gluterimide derivatives **1** provided dehalogenated products and carbonyl reduction was not observed.
8. Georgoulis, C.; Valery, J. M. *Synthesis* **1978**, 402.
9. Reactions of **1** and **2a** with tri-*n*-butyltin hydride and AIBN under high dilution condition produced deiodinated reduction products in quantitative yields. Thus, the possibility of radical cyclization was disregarded. For radical cyclization and ring expansion reaction of 2-haloalkyl-1,3-dicarbonyl systems, see: (a) Dowd, P.; Choi, S. C. *J. Am. Chem. Soc.* **1987**, *109*, 6548. (b) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565.

Permeation Control of Polymerized Liposome

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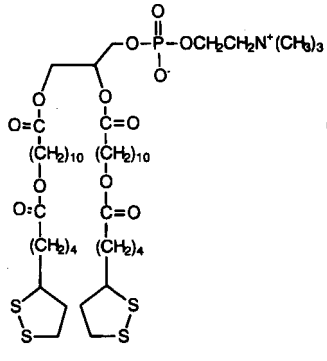
Received May 21, 1997

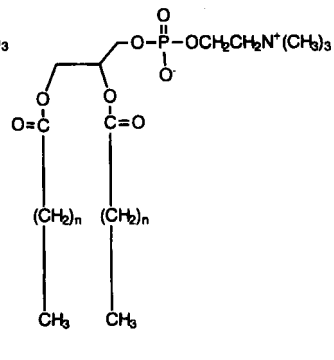
Liposomes are well-known as biomimetic materials applicable to drug delivery,[1] inhibitors of cell adhesion,[2] solar energy conversion, and biomembrane models. Polymerized liposomes have been suggested later as a better choice because of increased stability conferred by cross-linking hydrocarbon chain or head group,[3-5] low probability of lipid exchange and fusion, and the possibility of modifying liposome surface with recognition molecules like antibody, chelating agent.

In this paper we show very simple and easy way of controlling the permeability of our polymerizable lipid (PL). The synthesis of polymerizable phospholipid, 1,2-bis[12-(lipoyloxy)dodecanoyl]-*sn*-glycero-3-phosphorylcholine (**DLL**), was reported elsewhere and synthesized similarly.[6,7]

DLL is superior in drug delivery system to other PL's reported so far in many respects: First, polymerization does not require any harsh conditions like UV light, thermal energy for initiation, and any catalytic materials, mildly proceeding well just by slight pH increase (6.5 to 8.4) in the presence of 5 mol% of cysteine or other thiol-containing material. Second, only 3 hrs of shaking at room temperature is enough for polymerization up to 90%. Third, phospholipid itself is also a major component of biological membrane, and DLL's similar head group structure to natural membrane suggests some biocompatibility. Fourth, the degree of polymerization can be controlled by adjusting pH, and duration of reaction, together with the control of permeability. Fifth, the size of PL can be easily controlled by selecting the appropriate pore size filter before polymerization, and PL can retain the initial size after polymerization for a long period.



DLL



DMPC(n=12), DPPC(n=14)

Among the wide variety of liposome preparation methods, we prefer extrusion to other methods, especially sonication, for the reasons listed below. First, the sonic energy might disrupt the encapsulated biomolecule. Second, SUV (small unilamellar vesicle) prepared by sonication method is quite small for encapsulating drug or vaccine, and has sharper curvature which might give extra strain to the membrane structure, resulting in the loss of flexibility of membrane. Third, sonic method is not good for controlling the size of liposomes, leaving particles coming from the probe.

Accordingly, preparation of PL was done by extrusion method, using extruder from Lipex Biomembrane, Canada. Usually, 3 mg of DLL or DLL with other additives like 1,2-Dipalmitoyl-sn-glycero-3-phosphorylcholine (**DPPC**), and 1,