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Non-Toxic Ligands in Samarium Diiodide-Mediated Cyclizations

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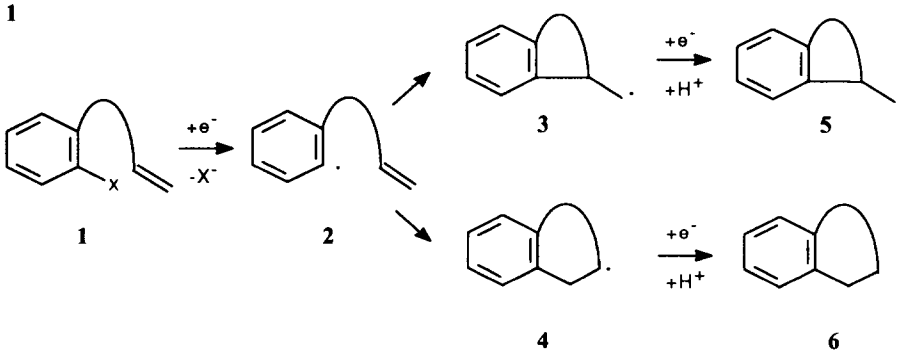
Abstract: Samarium diiodide-mediated cyclizations of aryl radicals carried out in the presence of several nitrogen ligands (triethylamine, 1,8-diazabyciclo[5.4.0]undec-7-ene and 1,1-3,3-Tetramethylguanidine) are described. The yields and the selectivities observed are comparable to the ones obtained by using hexamethylphosphoramide.

The success of samarium(II) complexes as single-electron reducing agents have been determined by the good chemo- and stereoselectivity observed under mild reaction conditions.[1] However, the reducing power of the most popular samarium(II) complex, SmI_2 in THF, is not always enough for an effective generation or trap of carbon radicals.[2]

Considering the cyclization process described in Scheme 1, high yields can be obtained only if the generation of the aryl radical (**1** → **2**) and the alkyl radical trap (**3** → **5** or **4** → **6**) are efficient.

Scheme 1

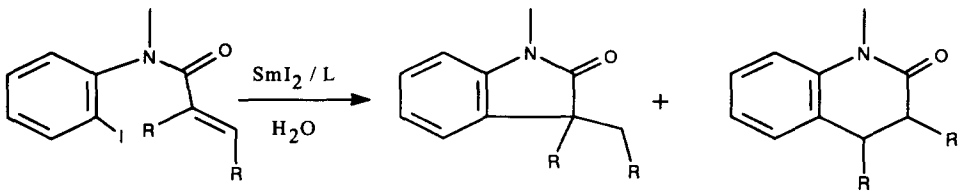


In this context, the formation of aryl radicals from the corresponding aryl iodides or aryl bromides using SmI_2 must be carried out in the presence of hexamethylphosphoramide (HMPA).[3,4] However, because of the toxicity of HMPA, studies on other samarium(II) additives have been carried out by several researchers.[1,5]

We report herein our preliminary results on the use of strong electron donor ligands in SmI_2-mediated aryl radical cyclizations focusing our attention on the use of commercially available nitrogen ligands to increase the reducing power of SmI_2 in THF.

Aryl iodides **7a,b**[6] were chosen to test the nitrogen ligands effect on the cyclization process and to investigate the chemoselectivity of the reaction. In fact, SmI_2 in the presence of additives is able to reduce unsaturated amides and esters.[5d]

Table 1. Samarium diiodide-mediated cyclization of **7a** and **7b**. Nitrogen ligands effect.[a]



7a,b **8a,b** **9a,b**

a: R= -$(CH_2)_4$-; **b**: R=CH_3

Entry	Substrate	Ligand (L/Sm)[b]	T °C	t h[c]	Conversion %[d]	8/9[d]	8+9 Yield, %[e]
1	**7a**	-	rt	19	68[f]	75/25	35
2	**7a**	HMPA(2)	-18	4	92	81/19	71
3	**7a**	DBU(2)	-18	-	100	73/27	75
4	**7a**	Et_3N(2)	-18	1	100	70/30	73
5	**7a**	TMG(1)	-18	1	85	70/30	64
6	**7a**	TMG(2)	-18	1.5	100	76/24	81
7	**7a**	TMG(4)	-18	0.5	100	83/17	85
8	**7a**	TMG(8)	-18	0.5	100	82/18	85
9	**7b**	-	rt	24	78[g]	28/72	41
10	**7b**	HMPA(2)	-18	2.5	100	48/52	68
11	**7b**	DBU(2)	-18	-	100	32/68	70
12	**7b**	Et_3N(2)	-18	1	100	30/70	61
13	**7b**	TMG(2)	-18	1	100	29/71	68

a) See ref 7. b) Molar ratio between the added ligand and the SmI_2 complex. c) Reaction time after complete addition of the substrate. d) Determined by GC and ^1H NMR (N-CH_3). e) Isolated yields. The ratio between the two diastereoisomers of **9a** ranged from 80/20 to 85/15. The ratio between the two diastereoisomers of **9b** ranged from 83/17 to 91/9. f) The product reduced at the double bond and dehalogenated was the 16% of the final mixture. g) The dehalogenated product was the 27% of the final reaction mixture.

Partial conversions were obtained in the absence of ligands at rt (Table 1, entries 1 and 9). On the other hand, an acceleration of the reaction rate was observed when HMPA (entry 2 and 10), 1,8-diazabyciclo[5.4.0]undec-7-ene [DBU] (entries 3 and 11), Et_3N (entries 4 and 12) and 1,1-3,3-tetramethylguanidine [TMG] (entries 5-8 and 13) were added. In fact, the cyclizations were almost complete after addition of the substrate at -18 °C and compounds **8** and **9** were isolated in good yields.[7,8] It is worth noting that the results obtained with Et_3N, DBU or TMG were even superior to the ones obtained with HMPA. Furthermore, in the presence of ligands, the side products that came from the reduction of the double bond and subsequent dehalogenation or direct dehalogenation of **7** were only a few percent of the final reaction mixture.

The ligand/SmI_2 molar ratio has practically no effect on the reaction course if more than 2 equivalents of ligands are present. In fact, only a slight modification of the yields and the 5-exo/6-endo selectivity was observed when the TMG/SmI_2 molar ratio was higher than 2 (entries 6-8).

The 5-exo *versus* 6-endo (**8a/9a**) selectivities observed in the cyclizations of compound **7a** (entries 1-6) were similar to the ones reported by Jones.[6a,c] On the contrary, the preference for the 6-endo cyclization product **9b** observed in the cyclizations of compound **7b** was unexpected (entries 7-11). In fact, the corresponding radical cyclization promoted by Co(I)-complexes affords preferentially the 5-exo products.[6d] Blank experiments, carried out in the absence of SmI_2, allowed to rule out the possible isomerization of the double bond of the starting material **7a,b** due to the presence of the additives. Therefore, compound **9** was not formed by a 6-exo cyclization from the corresponding β-γ unsaturated amide. On the other hand, a slow radical trap (**3** → **5**) could favor the formation of **9b** by rearrangement of the radical intermediate that come from the 5-exo cyclization process.[10] This mechanistic hypothesis is currently under investigation.

In contrast to the results described in Table 1, the reaction carried out using the corresponding aryl bromides gave consistent quantities of side products.[11] Without ligands partial conversions (≈30%) and poor yields (≈10%) were obtained. On the contrary, in the presence of DBU or TMG, complete conversions and moderate yields of compounds **8** and **9** (≈50%) were obtained. The 5-exo/6-endo ratios were similar to the ones reported in Table 1.

Summing up, the use of non-toxic nitrogen ligands (Et_3N, DBU and TMG) instead of HMPA gave promising results in samarium diiodide-mediated cyclizations. In particular good yields and chemoselectivities were obtained using aryl iodide derivatives as starting materials.

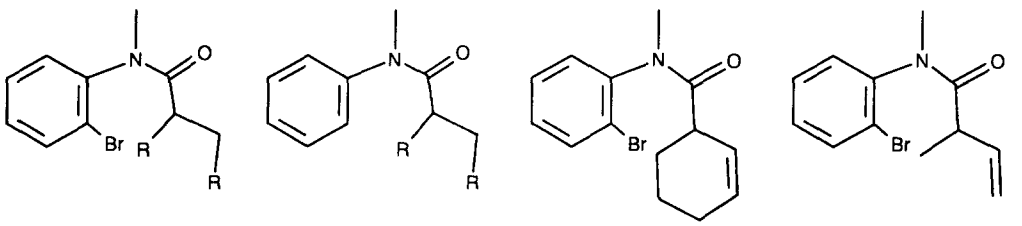
Further studies are under way in order to determine the scope and limitations of nitrogen ligands in SmI_2-mediated reactions.

Acknowledgement. We thank Dr. Sergio Penco for helpful and stimulating discussions.

References and Notes

1. Recent reviews and overviews: (a) Kagan,H.B. *New J. Chem.* **1990**, *14*, 453. (b) Molander,G.A. in *Comprehensive Organic Synthesis*; Trost,B.M., Fleming,I., Schreiber,S.L., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 251. (c) Soderquist,J.A. *Aldrichimica Acta* **1991**, *24*, 15. (c) Molander,G.A. *Chem. Rev.* **1992**, *92*, 29. (d) Curran,D.P.; Fevig,T.L.; Jasperse,C.P.; Totleben,M.J. *Synlett* **1992**, 943.
2. For a discussion on the reducing power of the samarium(II) complexes see ref 1d.
3. Inanaga,J.; Ishikawa,M.; Yamaguchi,M. *Chem. Lett.* **1987**, 1485.

4. The X-rays structure of $SmI_2(HMPA)_4$ has been recently reported. See: Hou,Z.; Wakatsuki,Y. *J. Chem. Soc. Chem. Commun.* **1994**, 1205.
5. DMPU: a) Bennett,S.M.; Larouche,D. *Synlett* **1991**, 805. b) Hasegawa,E.; Curran,D.P. *J. Org. Chem.* **1993**, *58*, 5008. 1,10-Phenanthroline was reported to suppress the aryl radical cyclization described in Scheme 1. See: c) Namy.J.L.; Collin,J.; Kagan,H.B. *Synlett* **1992**, 733. Other researchers reported the use of bidentate and tridentate nitrogen ligands in samarium-mediated reduction of electron poor olefins. See:d) Inanaga,J.; Sakai,S.; Handa,Y.; Yamaguchi,M.; Yokoyama,Y. *Chem. Lett.* **1991**, 2117.
6. The radical cyclization of **7a,b** and other related substrates was carried out in the presence of nBu_3SnH and Co(I) complexes. nBu_3SnH: a) Jones,K.; Thompson,M.; Wright,C. *J. Chem. Soc. Chem. Commun.* **1986**, 115. b) Bowman,W.; Heaney,H.; Jordan,B.M. *Tetrahedron Lett.* **1988**, *29*, 6657. Co(II): c) Clark,A.J.;Jones,K. *Tetrahedron Lett.* **1989**, *30*, 5485. d) Clark,A.J.; Jones,K. *Tetrahedron* **1992**, *48*, 6875. e) Clark, A.J.; Davies,D.I., Jones,K.; Millbanks,C. *J. Chem. Soc. Chem. Commun.* **1994**, 41.
7. Representative procedure. Table 1 entry 3. DBU (0.742mL, 4.92mmol) was added to a SmI_2 0.1mol THF solution[9] (24.6mL) at -18°C under argon. After, 5min a solution of **7a** (280mg, 0.82mmol) and H_2O (0.044mL, 2.46mmol) in THF (25mL) was dropwise added over a period of 3.5h. After an additional 1h stirring the mixture was treated with HCl 1mol% in water and extracted with AcOEt. After standard work up the crude was purified by flash chromatography affording 133mg of a 73/27 mixture of **8a** and **9a** (75% yield).
8. All compounds were identified by comparison with authentical samples.[6]
9. Girard,P.; Namy,J.L.; Kagan,H.B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
10. Bowman,W.R.; Westlake,P.J. *Tetrahedron* **1992**, *48*, 4027.
11. Typical side products are:



In contrast to the results obtained with **7a,b** (Table 1, entries 1 and 9), partial formation of the β-γ unsaturated amides from the corresponding aryl bromides was observed in the absence of additives.

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