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Samarium Diiodide Mediated Reduction of Allyl Halides. A New Reductive Approach to Exomethylene Cephams.

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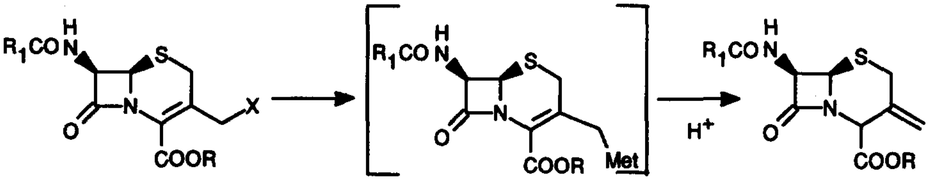
Abstract: *A new method for the synthesis of exomethylene cepham based on the use of samarium diiodide is described. The reaction proved to be chemo-, regio-, and stereo-selective affording the exomethylene cephams possessing the natural configuration at C-4 in high yields .*

Exomethylene cephams are key intermediates in the synthesis of therapeutically important cephalosporin antibiotics[1] and, over the years, several research groups have been involved in the development of new approaches to their synthesis.[2]

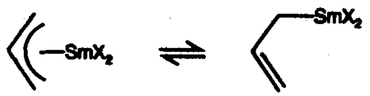
From a mechanistic point of view, all the reductive rearrangements to exomethylene cephams that use as starting material 3'-substituted cephems appear to be based on the formation of organometallic σ-complexes, that in the presence of a proton source by a SE2' reaction afford the desired products (Scheme 1).

Scheme 1



Herein we wish to report our results on a new practical reductive method for the synthesis of exomethylene cepham based on the use of samarium diiodide in the presence of a suitable proton source.

After Kagan's pioneering studies,[3] several papers on the use of samarium(II) complexes promoted reactions in organic synthesis appeared in the literature.[4] In particular, samarium(II) is able to generate allylsamarium(III) complexes starting from the corresponding allyl halides.[5] The π- and the σ-complexes are in equilibrium.



π-complex σ-complex

Our working hypothesis was based on the observation that in the case of 3'-halo cephems **1a-d**, the intramolecular coordination of the carbonyl moiety should stabilize the σ-complex **3a-d**.[6] Furthermore, the coordination of the oxygen of the proton source onto the metal can favor the formation of exomethylene derivatives **6a-d** through intermediates **5a-d**.

We have carried out preliminary studies using readily available 3'-halo cephems **1a-d**.[7,8,9] Among the proton sources used in the reductive rearrangement of 3'-chloro cephem **1a** (Table 1, entries 1-3), H_2O gave the best performance in terms of selectivity and yield (entry 3).[10] It is worth noting that exomethylene cepham **6a** with the natural configuration at C-4 was the only product present in the final mixture.[11] The reaction outcome was not dependent on the reaction temperature (entries 3-5) and several protective groups were compatible with the samarium diiodide reductive rearrangement. In fact, compounds **1b-d** afforded the target products **6b-d** in moderate to good yields (entries 6-9). The lower yields observed using 3'-iodo cephems **1c-d** were probably related to the instability of these compounds.[9]

It is worth noting that the stepwise reduction of **1a-d** is very fast (1→2→3). When the reaction was carried out by reverse addition procedure at -78°C, the blue color, indicating the presence of unreacted SmI_2, became persistent after addition of 2 equivalents of the metal complex (entry 10).

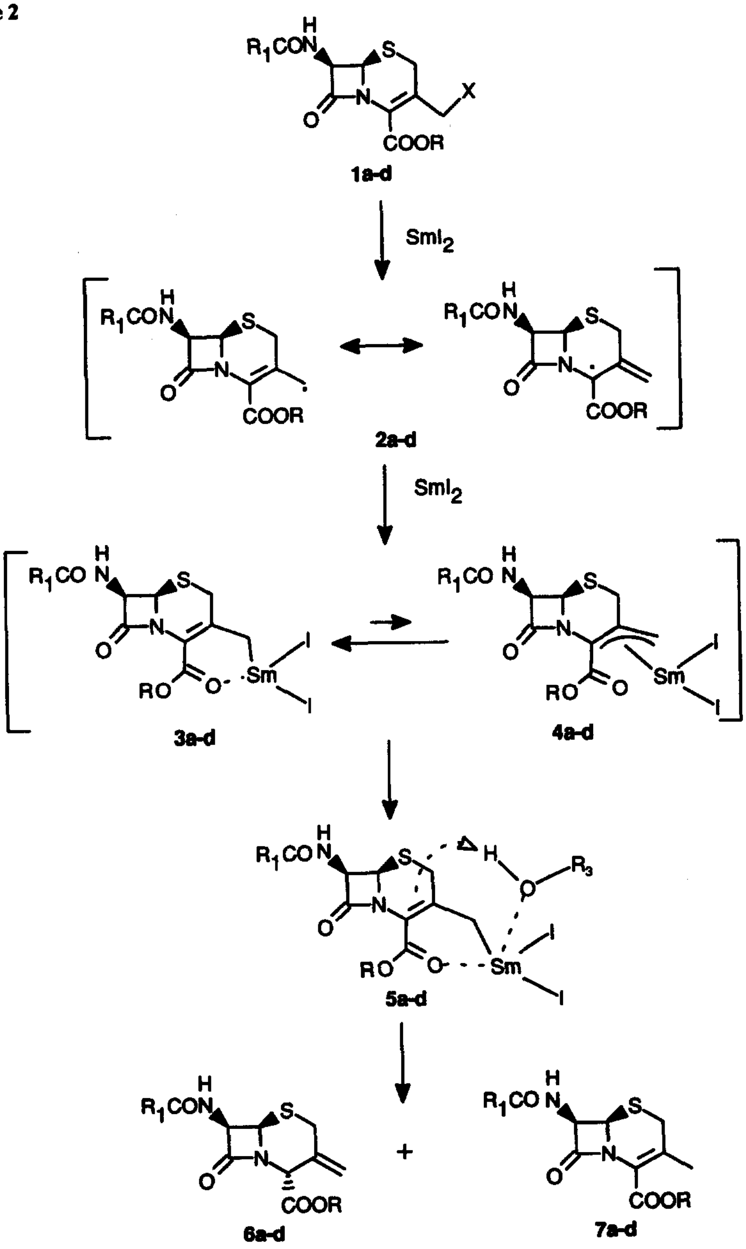
Table 1. Samarium diiodide reduction of 3'-halo cephem derivatives **1a-d**.[a]

Entry	**Substrate**	**Proton Source**	T °C	6/7[b]	**Product (Yields, %)**[c]
1	**1a**	t-BuOH	-78→rt	89/11	**6a+7a(77)**
2	**1a**	CH_3OH	-78→rt	68/32	**6a+7a(74)**
3	**1a**	H_2O	-78→rt	>97/3	**6a(84)**
4	**1a**	H_2O	-20→rt	>97/3	**6a(86)**
5	**1a**	H_2O	rt	>97/3	**6a(78)**
6	**1b**	H_2O	rt	>97/3	**6b(85)**
7	**1c**	H_2O	rt	>97/3	**6c(54)**[d]
8	**1c**	H_2O	-78→rt	>97/3	**6c(74)**[d]
9	**1d**	H_2O	-78→rt	>97/3	**6d(62)**[d]
10[e]	**1a**	H_2O	-78→rt	>97/3	**6a(78)**

a. See ref 10. b. The 6/7 ratios were determined by ^1H NMR (200MHz) of the crude. The notation >97/3 was used when compound 7 was not detected. c. Isolated yields. d. The yields were calculated taking into consideration the ≈95% assay of **1c-d**. See ref 9. e. The reaction was carried out by a reverse addition procedure. SmI_2 and H_2O were sequentially added to the solution of **1a** at -78°C .

Further studies are under way in order to extend this approach to the synthesis of new cephalosporin derivatives by samarium mediated carbon-carbon bond formation reactions.[4]

Scheme 2



X	R	R_1	
Cl	4-MeO-$PhCH_2$	$PhCH_2$	a
Cl	Ph_2CH	Ph	b
I	CH_3	$PhOCH_2$	c
I	CH_3	Ph	d

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6. For intramolecular coordination of carbonyl moieties in samarium(III) complexes see: (a) Fukuzawa,S.; Fujinami,T.; Sakai,S. *J. Chem. Soc. Chem. Commun.* **1986**,475. (b) Molander,G.A.; Kenny,C. *J. Org. Chem.* **1991**,*56*,1439. (c) Chiara,J.L.; Cabri,W.; Hanessian,S. *Tetrahedron Lett.* **1991**,*32*,1125.
7. 3'-Chloro cephem **1a** was purchased from Otsuka Chemical Co.,Ltd., Japan.
8. 3'-Chloro cephem **1b** was synthesized starting from deacetyl 7-aminocephalosporanic acid. See: Yamanaka,H.; Chiba,T.; Kawabata,K.; Takasugi,H.; Masugi,T.; Takaya,T. *J. Antibiotics* **1985**,*38*,1738.
9. 3'-Iodo cephems **1c-d** (assay ≈95%) were obtained by treatment of the corresponding acetate with 1.1 eq of $(CH_3)_3SiI$ at rt in CH_2Cl_2 for 1.5h. See: Bonjouklian,R.; Phillips,M.L. *Tetrahedron Lett.* **1981**,*22*,3915. Taking into consideration the instability of **1c-d** the crudes obtained from the iodination reaction were used directly in the subsequent reductive rearrangement.
10. Representative procedure. Table 1 entry 3. A solution of **1b** (486mg, 1mmol) and H_2O (0.054mL, 3mmol) in THF (28mL) was added over a period of 10 min to a SmI_2 0.1mol THF solution[3] (25mL) at -78°C under argon. Then, the cooling bath was removed and at rt the mixture was diluted with HCl 1mol% in water and extracted with ethyl acetate. After standard work up the crude was purified by flash chromatography (hexane/ethyl acetate 6/4 by volume) affording 380mg of **6a** (84% yield).
11. All products were characterized and identified by comparison with authentic samples. Compounds **6a-d** were synthesized following the method of ref. 2h. Compounds **7a-d** were synthesized by standard procedures from 7-ADCA.

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