

REDUCTIONS OF CARBOXYLIC ACIDS AND THEIR DERIVATIVES USING SAMARIUM DIODIDE-ACID SYSTEM

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Abstract: Carboxylic acid was converted to alcohol in a facile-rapid reduction using samarium diiodide in protic solvent under a basic or acidic medium at room temperature in high yield. A similar reaction of ester and anhydride reduced to the corresponding alcohol as the major products and nitrile afforded amine. Amide was rapidly reduced under a basic medium to afford alcohol, but the reduction with samarium diiodide-acid system of amide gave aldehyde in quantitative yield.

Introduction

In the growing field of divalent lanthanides, the use of samarium diiodide (SmI_2) as reducing agent in organic chemistry has been the subject of continuous interest. SmI_2 has proven to be a very useful and versatile reagent, and many applications¹ in organic synthesis have been published since the pioneering work of Kagan and co-workers.^{2,3} However, it is known that carboxylic acid, ester, amide, and nitrile functions are not easy to reduce with SmI_2 .⁴ Generally, carboxylic acids resist except for reduction by hydrides since carboxyl functionality is one of the highest oxidation states in other organic functionalities, although conversion of carboxylic acids into alcohols is usually important in synthetic chemistry. We investigated the use of SmI_2 -base system as a reducing reagent for carboxylic acids. It is interesting to point out that SmI_2 presents a high coordination number, a great affinity for oxygen atoms, and a reduction potential which is the highest among species soluble in an organic medium. The single-electron donor ability of Sm^{2+} is strongly affected by the nature of the ligands around Sm^{2+} . It has been surmised that the reducing ability can greatly be enhanced by the addition of a base to SmI_2 , such as KOH, LiNH_2 and LiOCH_3 , and the

reduction of carboxylic acids has been facilitated by SmI_2 -base system leading to alcohol.⁵ This system reduced amides and other carbonyl compounds.⁶ Thus, it was interesting to investigate the effect on the reducing power of SmI_2 with the additives. We were attracted attention to the properties of the lanthanides such as those with a high coordination number to form easily suitable chelate, and investigated the reactivity of SmI_2 by the addition of a variety of acids or bases on the organic functionalities.

Result and Discussion

Reduction of Carboxylic Acid, Ester and Anhydride with SmI_2 -Acid System. We found that the addition of a base highly accelerates the single-electron donor ability of SmI_2 , and this system rapidly reduced a variety of organic functionalities.^{5,6} In a series of studies on the reactivity of SmI_2 with an additive, the combination of SmI_2 with an acid has been firstly employed to reduce benzoic acid (1) in THF-protic solvent (Table I).

Table I. Reduction of Benzoic Acid (1)^{a)} with SmI_2 ^{b)}-Acid^{c)} System^{d)}

Acid	Time	Yield ^{d)} (%)	Acid	Time	Yield ^{d)} (%)	Acid	Time	Yield ^{d)} (%)
85% H_3PO_4	3 sec	91	P_2O_5	40 min	3	98% H_2SO_4	90 min	6
99% H_3PO_4	12 min	20	POCl_3	3 sec	0	H_3BO_3 ^{f)}	8 min	47
$\text{H}_4\text{P}_2\text{O}_7$ ^{f)}	3 sec	68	HCl -ether ^{h)}	3 sec	88	AlCl_3 ^{f)}	3 sec	62
$\text{H}_4\text{P}_2\text{O}_7$	60 min	16	35% HCl	3 sec	75	FeCl_3 ^{f)}	13 min	23
P_2O_5 ^{g)}	10 min	29	85% H_2SO_4	3 sec	48	NH_4Cl ^{f)}	60 sec	53

a) Benzoic acid (1); 0.5 mmol. b) SmI_2 ; 2 mmol, 0.1 M in THF. c) Acid; 1 mmol d) Reactions were carried out at room temperature under argon. e) Isolated yields of PhCH_2OH (12). f) 0.5 ml of H_2O was added. g) 0.5 ml of methanol was added. h) 10 ml of ether saturated HCl .

The SmI_2 -85% H_3PO_4 system yielded much better results than the other tested SmI_2 -acid systems, so we investigated the reduction of carboxylic acids, ester, acyl halide and anhydride with this system. The reduction of carboxylic acids (1 – 6) proceeded smoothly with this system at room temperature to afford the corresponding alcohols (12 – 17) in high yields. Interestingly, this system reduced pyridinecarboxylic acids (7 and 8) into the corresponding methylpyridines (18 and 19) under similar conditions. Ester (9) was also reduced into alcohol in good yield. On the other hand, the reduction of aliphatic carboxylic acids with as SmI_2 -base system had given alcohol in excellent yields.⁵ In spite of a variety of examinations, similar reactions of aliphatic carboxylic acids resulted in unsatisfactory yields. Anhydride (10) and acyl chloride (11) were also reduced with this system into alcohol (12) and the reductive C-C coupling products (21). A new SmI_2 -85% H_3PO_4 system rapidly reduced carboxylic acid, ester, anhydride and acyl halide under extremely mild conditions (Table II).

Table II. Reduction of Carboxylic Acids, Ester, and Anhydride with SmI_2 -85% H_3PO_4 System^{a)}

Substrate (No.)	Time (sec)	Product (No.)	Yield (%) ^{b)}
PhCOOH (1)	3	PhCH ₂ OH (12)	91
PhCOOH (1) ^{c)}	3	PhCH ₂ OH (12)	48
o-CH ₃ C ₆ H ₄ COOH (2)	4	o-CH ₃ C ₆ H ₄ CH ₂ OH (13)	91
p-CH ₃ C ₆ H ₄ COOH (3)	3	p-CH ₃ C ₆ H ₄ CH ₂ OH (14)	95
o-ClC ₆ H ₄ COOH (4)	3	o-ClC ₆ H ₄ CH ₂ OH (15)	97
m-ClC ₆ H ₄ COOH (5)	3	m-ClC ₆ H ₄ CH ₂ OH (16)	96
p-ClC ₆ H ₄ COOH (6)	3	p-ClC ₆ H ₄ CH ₂ OH (17)	94
2-PyCOOH (7) ^{d)}	3	2-PyCH ₃ (18) ^{c)}	43
4-PyCOOH (8) ^{d)}	3	4-PyCH ₃ (19) ^{c)}	48
PhCOOCH ₃ (9)	3	PhCH ₂ OH (12)	72
(PhCO) ₂ O (10) ^{e)}	3	PhCH ₂ OH (12) 46	PhCHO (20) 13
PhCOCl (11) ^{f)}	3	PhCH ₂ OH (12) 31	(PhCHOH) ₂ (21) 40

a) The reactions were carried out using 0.5 mmol of substrate, 2 mmol of SmI_2 (0.1 M in THF solution), and 0.5 ml of 85% H_3PO_4 at room temperature under argon. b) Isolated yield. c) SmI_2 ; 1 mmol. d) Py; pyridyl. e) By-products; 1,2-diphenyl-1,2-ethandiol (21) (9 %), 1,2-diphenylethanol (22 %). f) By-products; 1,2-diphenylethanol (14 %), benzoin (trace).

In general, reduction of carboxyl functionality offers certain difficulties in the presence of protic solvent with ordinary reducing agents under mild conditions. The reducing ability of SmI_2 can greatly be enhanced by the addition of protic acid or base, and its reduction proceeds with facility and rapidity in the protic solvent including water. In the reduction of SmI_2 -base system, the single-electron donor ability of Sm^{2+} becomes intense by the coordination of base to Sm^{2+} . The use of SmI_2 in the presence of an acid facilitates reduction for the lowering of reduction potential consequent upon the action of the acid to the substrate and further coordination of the conjugate base to Sm^{2+} . As described above, the addition of an acid or base in the reduction with SmI_2 proved to have a stronger reducing ability than the use of SmI_2 alone, and rapidly reduced carboxylic acids and their derivatives.

Reduction of Amides, Hydrazides, and Hydroxamic Acids with SmI_2 -Acid System. Little work has been reported on the reduction of amide with SmI_2 except for the our previous paper.⁶ We dealt with primary amides, hydrazides, and hydroxamic acids in an analogous procedure to use the acids as an additive. The results are tabulated in Tables III – V.

The reaction of benzamide (22) with SmI_2 in the absence of an acid gave only a trace of benzyl alcohol 12 and resulted in recovery of the starting material (Entry 1), and a similar reaction adding H_2O afforded alcohol 12 accompanied by a trace of amine (34) (Entry 2 and 3).

Table III. Reduction of Amides with SmI_2 -85% H_3PO_4 System^{a)}

Entry No.	Amide (No.)	SmI_2 ^{b)} mmol	85% H_3PO_4 ml	Time	Product (No.)	Yield ^{c)} (%)
1	PhCONH_2 (22)	4	none	8 h ^{d)}	PhCH_2OH (12)	3
2 ^{e)}	PhCONH_2 (22)	4	none	2 min	PhCH_2OH (12) PhCH_2NH_2 (34)	36 1
3 ^{f)}	PhCONH_2 (22)	8	none	90 min	PhCH_2OH (12) PhCH_2NH_2 (34)	63 1
4	PhCONH_2 (22)	4	1	3 sec	PhCHO (20)	>99
5	PhCONH_2 (22)	2	0.5	2 sec	PhCHO (20)	65
6	<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CONH}_2$ (23)	4	1	3 sec	<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CHO}$ (35)	90
7	<i>m</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CONH}_2$ (24)	4	1	3 sec	<i>m</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CHO}$ (36)	74
8	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CONH}_2$ (25)	4	1	3 sec	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CHO}$ (37)	91
9	<i>o</i> - $\text{HOC}_6\text{H}_4\text{CONH}_2$ (26)	4	1	3 sec	<i>o</i> - $\text{HOC}_6\text{H}_4\text{CHO}$ (38)	97
10	<i>o</i> - $\text{ClC}_6\text{H}_4\text{CONH}_2$ (27)	4	1	3 sec	<i>o</i> - $\text{ClC}_6\text{H}_4\text{CHO}$ (39)	>99
11	<i>m</i> - $\text{ClC}_6\text{H}_4\text{CONH}_2$ (28)	4	1	3 sec	<i>m</i> - $\text{ClC}_6\text{H}_4\text{CHO}$ (40)	>99
12	<i>p</i> - $\text{ClC}_6\text{H}_4\text{CONH}_2$ (29)	4	1	3 sec	<i>p</i> - $\text{ClC}_6\text{H}_4\text{CHO}$ (41)	>99
13	Piperonylamide (30)	4	1	3 sec	Piperonal (42)	>99
14	PhCONHPh (31)	4	1	3 sec	PhCH_2NPh (45) PhCHO (20) PhCH_2OH (12)	66 23 4
15	$\text{PhCH}_2\text{CONH}_2$ (32)	4	1	90 sec	PhCH_2CHO (43)	14
16	$\text{Ph}(\text{CH}_2)_2\text{CONH}_2$ (33)	4	1	4 min	$\text{Ph}(\text{CH}_2)_2\text{CHO}$ (44)	6

a) The reactions were carried out using 1 mmol of substrate at room temperature under argon. b) SmI_2 in THF (0.1 M). c) Isolated yield. d) Interrupted reaction time. e) 0.1 ml of H_2O was added. f) 0.2 ml of H_2O was added.

It was quite unexpected that treatment of amides with SmI_2 -acid system produced not alcohol but aldehyde. In order to examine the reducing ability of SmI_2 -acid systems toward amide, our first trial conducted with the reactions of benzamide **22** using 4 mol eq of SmI_2 in the presence of acids produced as follows: used acid (yield of aldehyde (**20**)), 85% H_3PO_4 (99%), 80% H_2SO_4 (66%), dry HCl -ether (68%), conc. HCl (59%), P_2O_5 (0%). In these reactions, amide **22** was rapidly reduced with the SmI_2 -85% H_3PO_4 system at room temperature into benzaldehyde **20** in a quantitative yield. Compared with the result by this system, the reductions with the other SmI_2 -acid systems gave aldehyde **20** in low yields accompanied by benzyl alcohol **12** and/or benzylamine **34**. Accordingly, it can be assumed that the SmI_2 -85% H_3PO_4 system is the most appropriate for the reduction of amide into aldehyde of the SmI_2 -acid systems tested. Aromatic amides (**22** - **33**) were rapidly reduced with SmI_2 (4 mol eq)-85% H_3PO_4 system to the corresponding aldehydes (**20** and **35** - **42**) at room temperature in quantitative

yields accompanied with a trace of amines. The yield of aldehyde **20** was decreased in a similar reaction of amide **22** using 2 mol eq of SmI_2 (Entry 5). Contrary to these results, similar reactions of aliphatic amides (**32** and **33**) with this system were unsatisfactory in the yields of aldehydes (**43** and **44**). For the difference of these observed aldehyde yields, the cause might be the difference in stability of the ketyl radicals, which are intermediates in the reducing process with SmI_2 ,^{1a} between aromatic amides and aliphatic amides.

As shown in Table IV, 2- and 4-pyridinecarboxamides (**46** and **47**) were rapidly reduced with this system to give 2- and 4-methylpyridines (**18** and **19**) as major products, respectively. These results are similar to the previous results, where the carboxyl and aldehyde moieties of benzoic acid derivatives were reduced into methyl group with SmI_2 -base system.

Table IV. Reduction of Pyridinecarboxamides (**46** and **47**) with SmI_2 -85% H_3PO_4 System^{a)}

Amide (No.)	SmI_2 ^{b)} (mmol)	85% H_3PO_4 (ml)	Time	Product (No.)			Yield (%) ^{c)}	
				Py-CHO	Py- CH_2OH	Py- CH_3		
(46)	1	none	1 min	(48) 10	(49) 17	—	—	—
(46)	2	none	35 min	(48) 24	(49) 62	—	—	—
(46)	2	0.2	2 sec	—	(49) 55	(18) 15		
(46)	4	0.5	2 sec	—	—	(18) 88		
(47)	1	none	40 sec	(50) 6	—	—	—	—
(47)	2	none	100 min	(50) 8	(51) 19	(19) trace		
(47)	2	0.2	3 sec	(50) 1	(51) 18	(19) 33		
(47)	4	0.5	3 sec	—	—	(19) 67		

a) The reactions were carried out using 0.5 mmol of substrate and 0.5 ml of 85% H_3PO_4 at room temperature under argon. b) SmI_2 in THF (0.1 M). c) Isolated yield.

Table V. Reduction of Hydrazides (**52** and **53**) and Hydroxamic acids (**54** and **55**) with SmI_2 -85% H_3PO_4 ^{a)}

Compound (No.)	SmI_2 ^{b)} (mmol)	85% H_3PO_4 (ml)	Time (sec)	Product (No.)	Yield (%) ^{c)}
PhCONHNH ₂ (52)	4	1	3	PhCHO (20)	81
				PhCONH ₂ (22)	17
o-HOC ₆ H ₄ CONHNH ₂ (53) ^{d)}	4	1	3	o-HOC ₆ H ₄ CHO (38)	48
				o-HOC ₆ H ₄ CONH ₂ (26)	50
PhCONHOH (54)	4	1	3	PhCHO (20)	91
				PhCONH ₂ (22)	6
o-HOC ₆ H ₄ CONHOH (55) ^{d)}	4	1	3	o-HOC ₆ H ₄ CHO (38)	59
				o-HOC ₆ H ₄ CONH ₂ (26)	40

a) The reactions were carried out using 1 mmol of substrate and 1 ml of 85% H_3PO_4 at room temperature under argon. b) SmI_2 in THF (0.1 M). c) Isolated yield. d) The substrate was dissolved in 6 ml of methanol.

In order to examine the reducing ability of this system toward the related functionalities of amide, hydrazides (**52** and **54**) and hydroxamic acids (**53** and **55**) were treated with this system under similar conditions. These compounds were similarly reduced with this system to give the corresponding aldehydes (**20** and **38**) and amides (**22** and **26**) (Table V).

The syntheses of aldehydes are more diverse and extensive than the syntheses of any other class for reasons of a reactive functional group and the middle of the different oxidation levels of organic compounds. Taking into account the utility of aldehydes as valuable intermediates, the discovery of truly milder and general synthetic methods has been desirable. On the other hand, primary amides are usually available by common synthetic methods. However, the conversion of amides to aldehydes is often difficult because of the further reactivity of the formed aldehyde to reduction. A few methods have been reported for the reduction of amides to aldehyde, such as the use of LiAlH_4 (tertiary amides),⁷ $\text{LiAlH}_2(\text{OEt})_2$ (tertiary amides),⁸ $\text{PCl}_5/\text{SnCl}_2$ (Sonn-Müller method, anilides of aromatic carboxylic acids)⁹ and Na-liq. NH_3 (tertiary amides).¹⁰ The reduction of primary amides into aldehydes with hydrides is not suitable because of the consumption of hydrides with active hydrogen. However, as described above, reports of the general direct reduction of primary and secondary amides to aldehydes have apparently not been published previously.

Treatment of amides with SmI_2 -acid system produced not alcohol but aldehyde, for which the present results differed from these preceding results⁶ and the striking characteristic of these reductions is the extremely short reaction time at room temperature. It is noteworthy that these reductions of aromatic amides into aldehydes can be rapidly performed under mild conditions in quantitative yields, so the SmI_2 -85% H_3PO_4 system provides a useful route for the direct synthesis of aromatic aldehydes from amides in synthetic chemistry.

Reduction of Nitrile with SmI_2 -Acid or Base System. Based on our previous observation that the electron transfer from SmI_2 was highly promoted by a coexisting base or acid, the present paper deals with the reduction of nitriles with SmI_2 -base or acid system.

Kagan and Namy reported that aliphatic and aromatic nitriles are unreactive toward SmI_2 .⁴ However, as shown in Tables VI and VII, both aromatic and aliphatic nitriles (**56** – **65**) were rapidly reduced with the SmI_2 -85% H_3PO_4 or 50% KOH system in the presence of H_2O at room temperature to the corresponding primary amines (**34** and **66** – **74**) in good yields. In these reductions, methanol was able to be used as a source except for H_2O . These reductions also proceeded with other acid- SmI_2 systems, such as HCl , H_2SO_4 , FeCl_3 , POCl_3 , P_2O_5 , and NH_4Cl , and with other base- SmI_2 systems, such as LiNH_2 , NaOH , tert-BuOK , $\text{Al}(\text{i-PrO})_3$, and LiOMe . In the reactions of *o*- and *p*-methylbenzonnitriles **57** and **58**, secondary amines (**75** and **76**) were also obtained as by-products under the similar conditions. When *o*- and *p*-chlorobenzonnitriles **59** and **60** were treated with SmI_2 -base system, the elimination of chloro moiety proceeded simultaneously to give benzylamine **34** as the major products. However, the chloro moiety of these nitriles was unreactive in the SmI_2 -85% H_3PO_4 system.

As described above, nitriles were smoothly reduced into only the corresponding primary amines, except for nitriles **57** and **58**, with both SmI_2 -base and acid systems at room temperature. In these reactions, the reductions with the SmI_2 -50% KOH system required 8 mol eq of SmI_2 in order to improve on the yields. Nitriles were reduced with SmI_2 -85% H_3PO_4 system using 4 mol eq of SmI_2 with a shorter reaction time in good yields.

Table VI. Reduction of Nitriles with SmI_2 -85% H_3PO_4 System^{a)}

RCN (No.)	Time	Product (No.)	Yield/% ^{b)}
$\text{C}_6\text{H}_5\text{CN}$ (56)	1 min	$\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$ (34)	81
$\text{C}_6\text{H}_5\text{CN}$ (56) ^{c)}	6 min	$\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$ (34)	99
<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CN}$ (57)	35 sec	<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{NH}_2$ (66)	52
		(<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2$) ₂ NH (75)	10
<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CN}$ (58)	10 sec	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{NH}_2$ (67)	55
		(<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2$) ₂ NH (76)	14
<i>o</i> - $\text{ClC}_6\text{H}_4\text{CN}$ (59)	5 sec	<i>o</i> - $\text{ClC}_6\text{H}_4\text{CH}_2\text{NH}_2$ (68)	76
<i>p</i> - $\text{ClC}_6\text{H}_4\text{CN}$ (60)	10 sec	<i>p</i> - $\text{ClC}_6\text{H}_4\text{CH}_2\text{NH}_2$ (69)	83
<i>o</i> - $\text{HOC}_6\text{H}_4\text{CN}$ (61)	30 sec	<i>o</i> - $\text{HOC}_6\text{H}_4\text{CH}_2\text{NH}_2$ (70)	90
<i>p</i> - $\text{HOC}_6\text{H}_4\text{CN}$ (62)	30 sec	<i>p</i> - $\text{HOC}_6\text{H}_4\text{CH}_2\text{NH}_2$ (71)	72
1-naphthonitrile (63)	10 sec	(1-naphthyl)methylamine (72)	71
2-naphthonitrile (64)	5 sec	(2-naphthyl)methylamine (73)	84
$\text{C}_6\text{H}_5\text{CH}_2\text{CN}$ (65)	50 sec	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}_2$ (74)	48

a) The reactions were carried out using 1 mmol of substrate, 4 mmol of SmI_2 (0.1 M in THF solution), and 1 ml of 85% H_3PO_4 at room temperature under argon. b) Isolated yield. c) SmI_2 8 mol^oeq.⁴ Benzonitrile 1 mmol.

Table VII. Reduction of Nitriles with SmI_2 -50% KOH System^{a)}

RCN (No.)	SmI_2 ^{b)} mol ² eq	Time min	Product (No.)		Yield/% ^{c)}	
			prim Amine	sec Amine	prim Amine	sec Amine
$\text{C}_6\text{H}_5\text{CN}$ (56)	4	5	(34)	78		
$\text{C}_6\text{H}_5\text{CN}$ (56)	8	25	(34)	91		
<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CN}$ (57)	4	2	(66)	58	(75)	8
<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CN}$ (57)	8	12	(66)	70	(75)	16
<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CN}$ (58)	4	6	(67)	64		
<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{CN}$ (58)	8	12	(67)	83	(76)	2
<i>o</i> - $\text{ClC}_6\text{H}_4\text{CN}$ (59)	4	3	(68)	26,	(34)	40
<i>o</i> - $\text{ClC}_6\text{H}_4\text{CN}$ (59)	8	4	(68)	6,	(34)	77
<i>p</i> - $\text{ClC}_6\text{H}_4\text{CN}$ (60)	4	5	(69)	39,	(34)	24
<i>p</i> - $\text{ClC}_6\text{H}_4\text{CN}$ (60)	8	3	(69)	12,	(34)	56

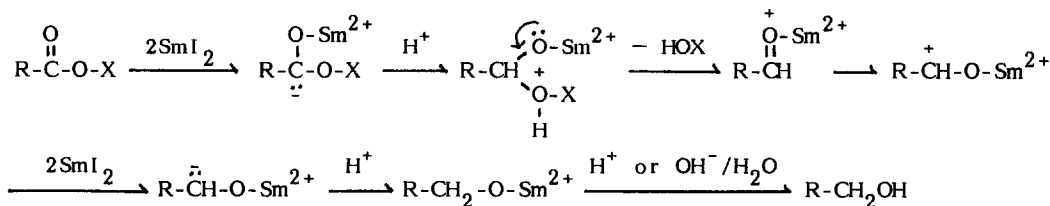
Table VII (continued)

RCN (No.)	SmI ₂ ^{b)} mol ² eq	Time min	Product (No.) Yield/% ^{c)}	
			prim Amine	sec Amine
o-HOC ₆ H ₄ CN (61)	4	2	(70)	58
o-HOC ₆ H ₄ CN (61)	8	9	(70)	88
p-HOC ₆ H ₄ CN (62)	4	1	(71)	36
p-HOC ₆ H ₄ CN (62)	8	10	(71)	81
1-naphthonitrile (63)	4	5	(72)	83
2-naphthonitrile (64)	4	4	(73)	86
C ₆ H ₅ CH ₂ CN (65)	4	35	(74)	58

a) The reactions were carried out using 1 mmol of substrate, and a molar ratio of SmI₂:50% KOH/1:2 at room temperature under argon. b) SmI₂ in THF (0.1 M). c) Isolated Yield.

Taking these results into account, it was considered that the reducing ability of the SmI₂-H₃PO₄ system was superior to that of the SmI₂-KOH system. These reductions can be rapidly performed under mild conditions, so the SmI₂-base and acid systems provide a useful new route for the direct reduction of nitriles into the corresponding primary amines in synthetic chemistry.

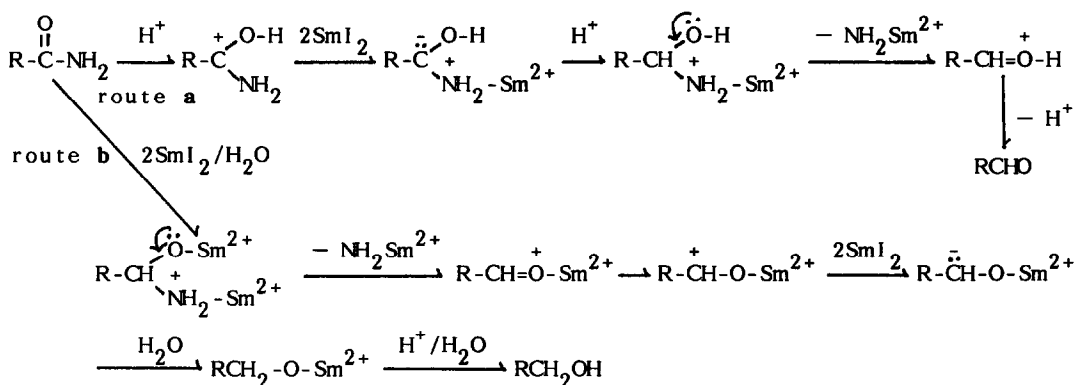
Mechanisms. In order to rationalize the formation of alcohol or aldehyde with the reduction of carboxylic acid and acyl derivatives, we propose the following reaction path: for an acidic medium on the reduction of carboxylic acid, ester, and acid anhydride with SmI₂ (Scheme 1) and reduction of amide with SmI₂-H₂O (route b in Scheme 2), the first step is the formation of a ketyl radical anion and O-Sm²⁺ bond with two electron donors from two equivalents of SmI₂. After the protonation of intermediate and elimination of H₂O, CH₃OH, PhCOOH, or NH₂Sm²⁺ from its protonated intermediate (RCH(O⁺HX)O-Sm²⁺ or RCH(N₃H₂Sm²⁺)O-Sm²⁺), an electron is further supplied by two equivalents of SmI₂. Finally, the O-Sm²⁺ bond cleaves by quenching of dil. HCl or dil. NaOH to furnish alcohol.



X: H, OCH₃, OCOPh

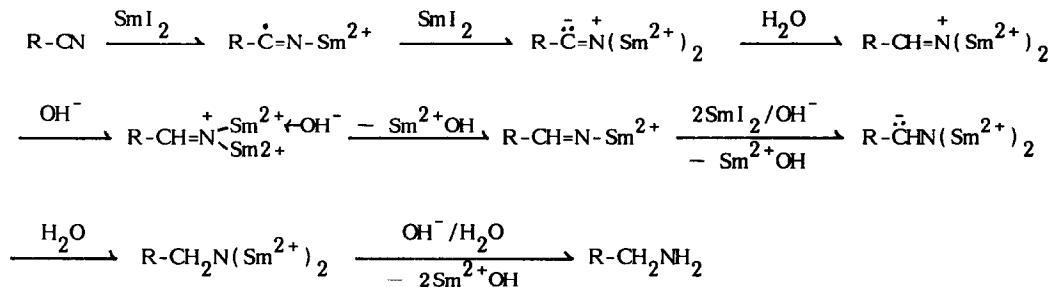
Scheme 1

On the other hand, amide is an extremely weak base, and therefore the protonation takes place in a strong acid medium and was performed not to the nitrogen but to the oxygen for the stability by the resonance. In the reduction of amide with SmI_2 -acid system, after two electrons transferred to the protonated intermediate from two equivalents of SmI_2 , Sm^{3+} combined with the nitrogen. Aldehyde forms by the final elimination of $\text{NH}_2\text{Sm}^{2+}$, as shown in route a of Scheme 2.



Scheme 2

The mechanism for the reduction of nitrile with SmI_2 -50% KOH system is proposed in Scheme 3. It seems that the addition of a base highly accelerates the electron transfer process of SmI_2 for the coordination of the base to Sm^{2+} . In the reduction with SmI_2 -85% H_3PO_4 system, H_3PO_4 may attack the cyano moiety of the nitrile to first produce the phosphorylated imine¹¹, and its imine is then reduced with SmI_2 to form amine, as shown in Scheme 4.



Scheme 3

The separating THF layer was taken up and aqueous layer was extracted twice with ether. The organic layer was washed with water and saturated NaCl solution and dried (MgSO_4), filtered and evaporated. The residue was purified by chromatographed on a silica column. Evaporation of the petroleum ether/benzene (90/10) gave a pure alcohol and it was characterized with authentic sample and by GC, GC/MS and IR spectra. In the case of anhydride (10) and acid chloride (11), reaction products furnished 12 to accompany such as the by-products of benzaldehyde, diol (21) and 1,2-diphenylethanol in the former and, 1,2-diphenylethanol and benzoin in the latter. The results are tabulated in Table II.

General Procedure for Reduction of Amide with SmI_2 -Acid System. In a typical procedure, a solution of 1 mmol of substrate dissolved in 1 ml of THF was added with use of a syringe pump to a solution of SmI_2 (0.1 M in THF, 4 mmol) and 85% H_3PO_4 (1 ml) was immediately added use of a syringe pump. The typical blue color of SmI_2 was immediately disappeared. After several minutes, 5% HCl (5 ml) was added to the resulting solution and was stirred for 5 minutes. The mixture was taken a salting out and the layers were separated. After the usual work up, crude product was purified by chromatographed on a neutral alumina column. Evaporation of the petroleum ether/benzene (90/10) gave a pure aldehyde and, furnished aldehydes (48 and 49), alcohols (49 and 51) and methylpyridines (18 and 19) from pyridinecarboxamides (46 and 47), and their were characterized with authentic sample and by GC, GC/MS and IR spectra. The results are tabulated in Table III.

General Procedure for Reduction of Hydrazides and Hydroxamic Acids with SmI_2 -Acid System. In a typical procedure, a solution of 1 mmol of substrate dissolved in 2 ml of THF was added with use of a syringe pump to a solution of SmI_2 (0.1 M in THF, 4 mmol) and 85% H_3PO_4 (1 ml) was immediately added use of a syringe pump. After the deep blue color of the reaction mixture changed to yellow green, treatment of the resulting solution in the same manner as the reaction of amide gave amine from hydrazide and amine accompanied with amide from hydroxamic acid. The results are tabulated in Table V.

General Procedure for Reduction of Nitriles with SmI_2 -Acid System. In a typical procedure, a solution of 1 mmol of substrate dissolved in 1 ml of THF was added with use of a syringe pump to a solution of SmI_2 (0.1 M in THF, 4 mmol) and 85% H_3PO_4 (1 ml) was immediately added use of a syringe pump. After the deep blue color of the reaction mixture changed to yellow green, conc. HCl (2 ml) was added to the resulting solution, and the THF was distilled off under reduced pressure. The residue was added 2 ml of H_2O , washed with ether, basified by the addition of 10% NaOH (NaHCO_3 in the cases of Phenolic nitriles (61 and 62)) and extracted with ether. After the usual work-up, the crude product was purified by chromatographed on a alumina column to give a pure primary amine, and afforded primary amine (66 or 67) and secondary amine (75 or 76) in the tolunitrile (57 or 58), and it was characterized with authentic sample and by GC, GC/MS and IR spectra. The results are tabulated in Table VI.

General Procedure for Reduction of Nitriles with SmI_2 -Base System. In a typical procedure, a solution of 1 mmol of substrate dissolved in 1 ml of THF was added with use of a syringe pump to a solution of SmI_2 (0.1 M in THF, 8 mmol) and 50% KOH (16 mmol) was immediately added use of a syringe pump. After the deep blue color of the reaction mixture changed to yellow green, conc. HCl (2 ml) was added to the resulting solution, and then treatment of the reaction mixture in the same manner as the reaction of nitriles with SmI_2 -base system afforded amine. The results are tabulated in Table VII.

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