



Pergamon

Tetrahedron Letters 41 (2000) 341–344

TETRAHEDRON
LETTERS

Novel and facile selective reduction of carboxylic acid with a samarium diiodide–lanthanide triflate–methanol–base system

Yasuko Kamochi* and Tadahiro Kudo

Daiichi College of Pharmaceutical Sciences, 22-1 Tamagawa-cho, Minami-ku, Fukuoka 815, Japan

Received 24 August 1999; revised 27 October 1999; accepted 29 October 1999

Abstract

The facile selective reduction of carboxylic acids in the presence of an aldehyde or that bearing a formyl group proceeded smoothly with a samarium diiodide–lanthanide triflate–methanol–base system at room temperature to give the corresponding alcohols in good to almost quantitative yield. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: selective reduction; samarium diiodide; lanthanide triflates; carboxylic acids; aldehydes; additives.

The selective reduction of carboxylic acid bearing other functional groups sensitive to ordinary reducing agents is a topic of much interest in synthetic chemistry. There is no efficient method for the direct selective reduction of carboxylic acid in the presence of an aldehyde or that bearing a formyl group. Generally, this transformation necessitates a three-step process of protection of the aldehyde moiety, reduction of carboxylic acid and, finally, liberation of the aldehyde moiety. Taking into account the utility of direct selective reduction of carboxylic acid in the presence of an aldehyde or that bearing a formyl group to alcohol, the development of a facile selective reduction method has been desirable from a synthetic viewpoint.

We reported previously that the electron transfer from samarium diiodide (SmI_2) was highly promoted in the presence of an additive, and carboxylic acids were reduced smoothly with this system.¹ In general, the direct selective reduction of carboxylic acid incurs certain difficulties in the co-existence of an aldehyde. However, it can be assumed that it is possible to perform the selective reduction of carboxylic acid in the co-existence of aldehyde with SmI_2 if acetalization of the aldehyde takes place immediately under the reduction conditions of carboxylic acid. Consequently, the present paper deals with a new selective reduction of carboxylic acid with a SmI_2 –samarium triflate ($\text{Sm}(\text{OTf})_3$)–MeOH–base system as the following method.

Our first trial was conducted with the acetalization of aldehydes in MeOH solution with lanthanide triflate ($\text{Ln}(\text{OTf})_3$) having the strong ability as a Lewis acid in the presence of water.² The acetalization of aldehydes proceeded rapidly with $\text{Ln}(\text{OTf})_3$ within five minutes at room temperature in almost

* Corresponding author. Tel: +81 92 541 0161; e-mail: kamochi@daiichi-cps.ac.jp (Y. Kamochi)

quantitative yield, and the esterification of carboxylic acid could have occurred only to an extent of 1% under similar conditions. The results of acetalization are tabulated in the References.³

Our next trial was conducted with the reaction of aldehyde and carboxylic acid with a SmI_2 - $\text{Sm}(\text{OTf})_3$ -MeOH-base system. As shown in Table 1, cyclohexanecarboxaldehyde was reduced with SmI_2 in THF-MeOH at room temperature in quantitative yield (entry 2). However, the reduction did not entirely proceed under similar conditions adding $\text{Sm}(\text{OTf})_3$ or with a SmI_2 - $\text{Sm}(\text{OTf})_3$ -MeOH-base system, and all of the aldehyde was recovered (entries 1 and 3). On the contrary, adding a MeOH solution of aldehyde into a THF solution of SmI_2 and $\text{Sm}(\text{OTf})_3$, the aldehyde was reduced rapidly in almost quantitative yield (entry 4). These results showed that the acetalization occurred immediately with the $\text{Sm}(\text{OTf})_3$ under the tested conditions. Contrary to these results, cyclohexanecarboxylic acid was reduced rapidly with the SmI_2 - $\text{Sm}(\text{OTf})_3$ -MeOH-base system (entry 6). Moreover, in the reduction of carboxylic acid with SmI_2 - $\text{Sm}(\text{OTf})_3$ -MeOH-base system, it can therefore be presumed that the reduction preferentially proceeded over acetalization of the aldehyde which is anticipated as a reduction intermediate.

Table 1
Reduction of cyclohexanecarboxaldehyde and cyclohexanecarboxylic acid with SmI_2 - $\text{Sm}(\text{OTf})_3$ -MeOH-base system^a

Entry	Substrate	SmI_2 eq mol	$\text{Sm}(\text{OTf})_3$ eq mol	20%KOH ml	Time min	Product Yield (%)		Recovery %
						 -CH ₂ OH	 -COOMe	
1	Cyclohexanecarboxaldehyde	2	0.4	none	40			> 99
2	Cyclohexanecarboxaldehyde	2	none	none	14	> 99		
3	Cyclohexanecarboxaldehyde	2	0.4	1	23			> 99
4	Cyclohexanecarboxaldehyde	2	0.4	1	1.4	95 ^c		
5	Cyclohexanecarboxylic acid	4	0.4	none	190		5	92
6	Cyclohexanecarboxylic acid	4	0.4	2	5	99		

a. A solution of the substrates (0.5 mmol) dissolved in methanol solution (5 ml) of $\text{Sm}(\text{OTf})_3$ was kept at room temperature for 5 min. The solution was added with a syringe pump to SmI_2 (0.1 M in THF) and 20% KOH was immediately added with a syringe pump with stirring under argon atmosphere at room temperature. After the typical blue color of SmI_2 disappeared and then removal of the solvent under reduced pressure, the residue was quenched with 10% HCl during 5 min following usual work-up. b. Isolated yield. c. The mixture of aldehyde and MeOH (5 ml) was added into a THF solution of SmI_2 and $\text{Sm}(\text{OTf})_3$, then 20% KOH was immediately added.

These results demonstrate that this system provides the possibility to selectively reduce carboxylic acids in the co-existence of an aldehyde or that bearing a formyl group. Therefore, we investigated the selective reduction of carboxylic acid in the following manner.

The reactions were carried out as follows: The aldehydes (0.5 mmol) and the carboxylic acids (0.5 mmol) were dissolved in methanol solution (5 ml) of $\text{Sm}(\text{OTf})_3$ (0.2 mmol) and the solution was kept at room temperature for five minutes. The solution was added with a syringe pump to SmI_2 (0.1 M in THF, 2 mmol) and 20% KOH (2 ml) or H_2O (1 ml) was immediately added with a syringe pump with stirring under an atmosphere of argon at room temperature. After the typical deep purple color of SmI_2 disappeared and then removal of the solvent under reduced pressure, the residue was quenched with 10% HCl (10 ml) during five minutes following usual work-up.

Irrespective of the presence of an aldehyde, only aliphatic carboxylic acids were reduced selectively to alcohols within a few minutes at room temperature in good to almost quantitative yield as shown in Table 2 (entries 1–7). α,β -Unsaturated carboxylic acid was reduced with this system using 6 equiv. mol of SmI_2 to give saturated alcohol in excellent yield (entry 9). Similarly, the selective reduction of aromatic carboxylic acids in the presence of an aldehyde or that bearing a formyl group, except for toluic acids

Table 2
 Selective reduction of carboxylic acids in the presence of an aldehyde or that bearing a formyl group
 with the SmI₂-Sm(OTf)₃-MeOH-base or H₂O system in THF^a

Entry	Substrate	Additive	ml	Time min	Reduction Product	Yield ^b %
1	Me(CH ₂) ₃ CH(C ₂ H ₅)COOH Me(CH ₂) ₇ CHO	KOH	2	8	Me(CH ₂) ₃ CH(C ₂ H ₅)CH ₂ OH Me(CH ₂) ₇ CH ₂ OH	93 1
2	Me(CH ₂) ₇ COOH Me(CH ₂) ₆ CHO	KOH	2	4.5	Me(CH ₂) ₇ CH ₂ OH Me(CH ₂) ₆ CH ₂ OH	96 3
3	Me(CH ₂) ₆ COOH Me(CH ₂) ₅ CHO	KOH	2	4.5	Me(CH ₂) ₆ CH ₂ OH	99 ^c
4	Cyclohexyl-COOH Me(CH ₂) ₄ CHO	KOH	2	4.5	Cyclohexyl-CH ₂ OH	99 ^c
5	(1-Me-cyclohexyl)-COOH Cyclohexyl-CHO	KOH	2	7	(1-Me-cyclohexyl)-CH ₂ OH Cyclohexyl-CH ₂ OH	82 8
6	(2-Me-cyclohexyl)-COOH Cyclohexyl-CHO	KOH	2	7	(2-Me-cyclohexyl)-CH ₂ OH Cyclohexyl-CH ₂ OH	84 10
7	CH ₂ =CH(CH ₂) ₇ COOH Me(CH ₂) ₇ CHO	KOH	2	5	CH ₂ =CH(CH ₂) ₇ CH ₂ OH Me(CH ₂) ₇ CH ₂ OH	96 trace
8	Me(CH ₂) ₆ CH=CHCOOH Me(CH ₂) ₅ CH=CHCHO	KOH	2	7	Me(CH ₂) ₈ CH ₂ OH Me(CH ₂) ₇ CH ₂ OH	49 ^d 8
9 ^e	Me(CH ₂) ₆ CH=CHCOOH Me(CH ₂) ₅ CH=CHCHO	KOH	2	15	Me(CH ₂) ₈ CH ₂ OH Me(CH ₂) ₇ CH ₂ OH	91 5
10	PhCOOH <i>p</i> -MeC ₆ H ₄ CHO	H ₂ O	2	6	PhCH ₂ OH	96 ^c
11	<i>m</i> -MeC ₆ H ₄ COOH PhCHO	H ₂ O	2	20	<i>m</i> -MeC ₆ H ₄ CH ₂ OH PhCH ₂ OH	67 7
12	<i>m</i> -MeC ₆ H ₄ COOH PhCHO	KOH	1	4	<i>m</i> -MeC ₆ H ₄ CH ₂ OH	93 ^c
13	<i>p</i> -MeC ₆ H ₄ COOH PhCHO	H ₂ O	2	28	<i>p</i> -MeC ₆ H ₄ CH ₂ OH PhCH ₂ OH	53 8
14	<i>p</i> -MeC ₆ H ₄ COOH PhCHO	KOH	1	5	<i>p</i> -MeC ₆ H ₄ CH ₂ OH PhCH ₂ OH	90 6
15	<i>m</i> -ClC ₆ H ₄ COOH PhCHO	H ₂ O	2	2	<i>m</i> -ClC ₆ H ₄ CH ₂ OH	>99 ^c
16	<i>p</i> -ClC ₆ H ₄ COOH PhCHO	H ₂ O	2	1	<i>p</i> -ClC ₆ H ₄ CH ₂ OH	99 ^c
17 ^f	<i>o</i> -OHCC ₆ H ₄ COOH	H ₂ O	2	5	<i>o</i> -OHCC ₆ H ₄ CH ₂ OH	98 ^c
18 ^f	<i>m</i> -OHCC ₆ H ₄ COOH	H ₂ O	2	9	<i>m</i> -OHCC ₆ H ₄ CH ₂ OH	93 ^c
19 ^f	<i>p</i> -OHCC ₆ H ₄ COOH	H ₂ O	2	6	<i>p</i> -OHCC ₆ H ₄ CH ₂ OH	95 ^c

a. A solution of the substrates (0.5 mmol of each substrate) dissolved in methanol solution (5 ml) of Sm(OTf)₃ (0.2 mmol) was kept at room temperature for 5 min. The solution was added into SmI₂ (2 mmol, 0.1 M in THF), then 20%KOH or H₂O was added immediately to the reaction mixture with stirring under argon atmosphere at room temperature. b. GC yield. The aldehydes were recovered in good to quantitative yield (entries 1~16). c. Isolated yield. d. By-product: Me(CH₂)₈COOH 37%. e. SmI₂: 3 mmol. f. A solution of the substrates (0.5 mmol) dissolved in methanol solution (5 ml) of Sm(OTf)₃ (0.2 mmol) was kept at room temperature for 5 min. The solution was added into SmI₂ (2 mmol, 0.1 M in THF), then H₂O was added immediately to the reaction mixture.

(entries 11 and 13), proceeded easily even by a similar system using water instead of KOH under mild conditions (entries 10 and 15–19). In addition, aldehydes were mostly unaffected by this system under the tested conditions.

In this method, though the actual reductant and the detailed mechanism of these selective reductions have not been clarified at the present stage, it has been surmised that the rapid acetalization of aldehyde proceeded with $\text{Sm}(\text{OTf})_3\text{-MeOH}$ at first. Subsequently, the reducing ability of SmI_2 can greatly be enhanced by the addition of an additive (KOH, MeOH and H_2O) to Sm^{2+} and the reduction of carboxylic acids has been facilitated by this system leading to alcohol.

Little work has been reported so far on the selective one-pot reduction of carboxylic acid in the presence of an aldehyde or that bearing a formyl group. As mentioned above, it can be presumed that the new $\text{SmI}_2\text{-Sm}(\text{OTf})_3\text{-MeOH-base/H}_2\text{O}$ system provides a useful and convenient method in synthetic chemistry for the selective one-pot reduction of carboxylic acid bearing a formyl group under mild conditions.

References

1. See for review and references cited therein: Kamochi, Y.; Kudo, T. *J. Syn. Org. Chem. Jpn.* **1994**, *52*, 45. Idem *Rev. Heteroatom Chem.* **1994**, *11*, 165. Idem *Chem. Lett.* **1991**, 893. Idem *Tetrahedron Lett.* **1991**, *32*, 3511. Idem *Tetrahedron* **1992**, *48*, 4301.
2. It has been reported that lanthanide triflates are found to be stable in aqueous solution and can act as strong Lewis acid catalysts. Kobayashi, S. *Chem. Lett.* **1991**, 2187. Kobayashi, S.; Hachiya, I. *Tetrahedron Lett.* **1992**, *33*, 1625. Idem *J. Org. Chem.* **1994**, *59*, 3590.
3. Luche et al. reported that lanthanide chlorides are efficient catalysts for the acetalization of aldehydes in the presence of trimethyl orthoformate as a water scavenger⁴ and also the lanthanide chloride–methanol–sodium borohydride system is used for selective reduction of ketones in the presence of aldehyde.⁵ Furthermore, Fukuzawa et al. achieved the chiral acetalization of carbonyl compounds catalyzed by $\text{Ln}(\text{OTf})_3$. However, these acetalizations necessitated long reaction time for 13 hours–2 days until completion of the reactions.⁶ We tested the rapid acetalization of aldehydes in MeOH solution with lanthanide triflates having the strong ability as a Lewis acid in the absence of a water scavenger as shown in Table 3.

Table 3
Acetalization and esterification with lanthanide triflate

Entry	Substrate		$\text{Ln}(\text{OTf})_3$ Ln	Product / Time / Yield (%) ^b			
	RCHO R	RCOOH R		Acetal			Ester
				1 min	3 min	5 min	5 min
1	Cyclohexyl		Sm	76	89	98	
2	Cyclohexyl		Er	80	95	96	
3	Cyclohexyl		Yb	73	82	92	
4	<i>n</i> -Heptyl		Sm			99	
5	<i>trans</i> -2-Heptenyl		Sm			89	
6	Phenyl		Sm			95	
7		Cyclohexyl	Sm				1 ^c

a. After substrate (0.5 mmol) was added to methanol (5 ml) solution of $\text{Ln}(\text{OTf})_3$ (0.4 eq mol), the solution was stirred for 5 min at room temperature. After removal of methanol, 10% K_2CO_3 was added to the residue and the usual treatment was carried out. b. Isolated yield. c. Recovery: 95%.

4. Luche, J. L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976.
5. Gemal, A. L.; Luche, J. L. *Tetrahedron Lett.* **1981**, *22*, 4077. Idem *J. Am. Chem. Soc.* **1979**, *101*, 5848. Idem *J. Org. Chem.* **1979**, *23*, 4187.
6. Fukuzawa, S.; Tsuchimoto, T.; Hotaka, T.; Hiyama, T. *Synlett* **1995**, 1077.