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Samarium Diiodide-Promoted Diiodomethylation of Carbonyl Compounds with Iodoform. Synthetic Applications of Diiodoalcohols

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Abstract: A rapid and effective diiodomethylation of carbonyl compounds using SmI_2 and iodoform is described. Transformations of the obtained diiodoalcohols **2** into α-iodoaldehydes **5** and α-hydroxyacids **6** is also reported. © 1998 Elsevier Science Ltd. All rights reserved.

Halomethylation of aldehydes or ketones is difficult to achieve using α-halogenated organometallic compounds due to their thermal instability.[1] Alternatively, a rapid and efficient iodomethylation of carbonyl compounds at about room temperature using samarium metal[2] or SmI_2[3] has been developed.

On the other hand, although many dichloro- or dibromomethylations of carbonyl compounds using organometallic compounds (Li, Mg) have been described,[4] examples of diiodomethylation of aldehydes or ketones are rare: only one is known.[5] Moreover, to our best knowledge, diiodomethylation of carbonyl compounds by means of SmI_2 or metallic samarium has not been reported in the literature to date.

The diiodomethylation of carbonyl compounds would afford β,β-diiodoalkanols, which are interesting building blocks in organic synthesis. In general, organoiodine compounds are extremely useful intermediates in ionic[6] and radical[7] organic reactions and in particular, 1,1-diiodoalkan-2-ols could be transformed into α-hydroxycarboxylic acids or α-iodoaldehydes, which are important because of their biological properties[8] or synthetic applications,[9] respectively.

Recently, we have reported the iodomethylation of chiral α-amino aldehydes by means of samarium metal and diiodomethane.[10] Herein we wish to report the rapid and effective diiodomethylation of carbonyl compounds using SmI_2 and iodoform and their further transformations into α-hydroxycarboxylic acids and α-iodoaldehydes.

Initially, diiodomethylation of carbonyl compounds was carried out by means of samarium metal and triiodomethane.[11] In this case, SmI_2 was generated *in situ* by reaction of iodoform with metallic samarium.[12] The subsequent reaction of SmI_2 with iodoform produces a diiodomethylsamarium reagent, which reacts with the corresponding aldehyde to afford the expected β,β-diiodoalcohol. However, the procedure has some drawbacks: aromatic aldehydes (Table 1, entries 1, 3-5) gave moderate to low yields; lower yields were obtained for aliphatic aldehydes (Table 1, entry 9); when ketones were used instead of aldehydes, the starting ketone was recovered (Table 1, entry 14) and addition of HMPA[13] as cosolvent afforded a complex mixture of products.

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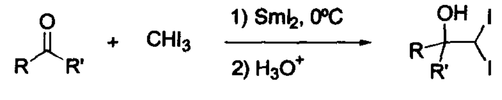
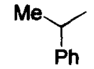
Diiodomethylation of carbonyl compounds was improved using preformed samarium iodide instead of metallic samarium. A typical procedure for the synthesis of diiodoalcohols **2** is as follows: to a solution of the corresponding aldehyde **1** (0.5 mmol) and iodoform (0.395 g, 1 mmol) in THF (18 mL) was added dropwise, under nitrogen, SmI_2 (0.1 M in THF, 2 mmol) at 0°C. Characteristic blue colour of samarium (II) disappears immediately after addition, but 45 min (see Table 1) are usually needed to complete reaction of the substrate. The resulting mixture was treated with 1 M HCl and after usual work-up, the corresponding crude diiodoalcohol was obtained. Flash column chromatography over silica gel (polarity gradient, from hexane to hexane/ethyl acetate 10/1) provided the pure product **2**.

Table 1: Synthesis of Diiodoalcohols



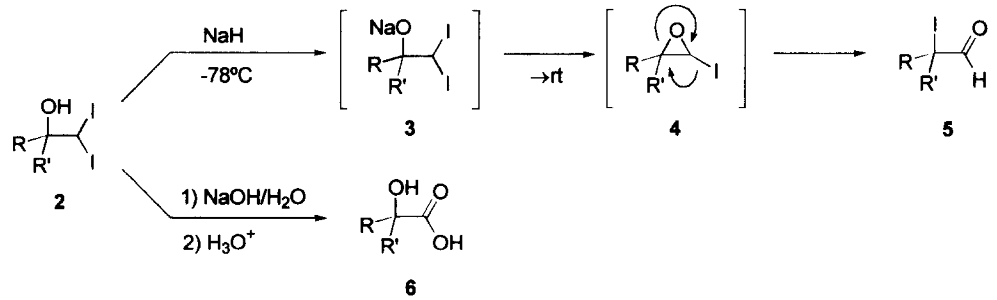
1 **2**

Entry	R	R'	Product	Method[a]	Temperature	Yield (%)[b]
1	Ph	H	**2a**	A	0°C	38
2	Ph	H	**2a**	B	0°C	61
3	4-Cl-C_6H_4	H	**2b**	A	25°C	30
4	4-Cl-C_6H_4	H	**2b**	A	0°C	40
5	4-Cl-C_6H_4	H	**2b**	A	-20°C	47
6	4-Cl-C_6H_4	H	**2b**	B	0°C	60
7	Furyl	H	**2c**	B	0°C	40
8		H	**2d**	B	0°C	58
9	Cyclohexyl	H	**2e**	A	0°C	23
10	Cyclohexyl	H	**2e**	B	0°C	62
11	C_6H_{13}	H	**2f**	B	0°C	60
12		H	**2g**	B	0°C	57[c]
13	-C_4H_8-		**2h**	B[d]	0°C	40
14	-C_5H_{10}-		**2h**	A[d]	0°C	no reaction
15	-C_5H_{10}-		**2h**	B[d]	0°C	49

[a] A: performed with Sm powder (see reference 11). B: performed with SmI_2 (see text). [b] Yield of pure compound (after chromatography) based on the starting carbonyl compound. [c] diastereoisomeric excess>98% (300 MHz ^{1}H-NMR spectroscopy). [d] Reaction time: 6 h.

As shown in Table 1 (method B), reasonable yields were obtained from aldehydes. The reaction of diiodomethylation is general for aldehydes: aromatics, α,β-unsaturated and lineal or ramified aliphatic aldehydes have been diiodomethylated. Interestingly, the diiodomethylation of 2-phenylpropanal (Table 1, entry 12) took place with total diastereoselectivity (NMR analysis of the crude product showed the presence of only one diastereomer). The assignment of the stereochemistry was carried out after conversion of **2g** into 3-phenyl-2-butanol, using Bu_3SnH,[14] obtaining the diastereoisomer *unlike*[15] or *erithro*. The observed diastereoselectivity is the same[16] as that previously reported for the iodomethylation of chiral α-amino aldehydes[10] and 2-phenylpropanal[3a] using Sm/CH_2I_2 or SmI_2, respectively. When diiodomethylation was performed with ketones, only cyclic ketones afforded the corresponding β,β-diiodoalcohols; in this case, the reaction time was longer and lower yield was obtained in comparison to aldehydes.

To prove the usefulness of compounds **2** in organic synthesis, based on the pronounced versatility of carbon-iodine bond, these compounds were transformed into α-iodoaldehydes or α-hydroxycarboxylic acids (see Scheme 1 and Table 2, entries 1-3). Thus, treatment of compounds 2 with NaH in CH_2Cl_2 at low temperature (-78°C) afforded (when temperature was allowed to reach room temperature) α-iodoaldehydes 5. As depicted in Scheme 2, the proposed mechanism involves the initial formation of the alcoholate 3 and the further nucleophilic displacement of iodine by oxygen yielding the iodoepoxide 4, that suffer a rearrangement affording the α-iodoaldehyde 5.[17]

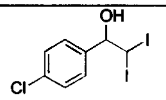
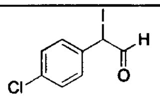
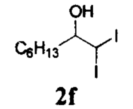
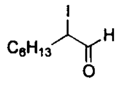
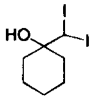
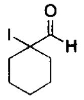
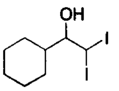
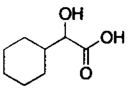
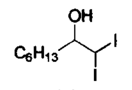
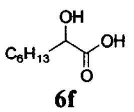


Scheme 1: Synthesis of α-iodoaldehydes and α-hydroxyacids

Although the yields for the iodoaldehydes prepared were high (crude product), these compounds are extremely unstable,[18] and suffer decomposition on air, light or silica gel. However, an analytical sample could be obtained by kugelrohr distillation at low pressure.

On the other hand, reaction of alcohols 2 with aqueous NaOH for 2 days at room temperature[19] gave the expected α-hydroxycarboxylic acid 6 (see Scheme 1 and Table 2, entries 4 and 5).

Table 2: Synthetic Applications of Diiodoalcohols 2

Entry	Substrate	Product	Yield (%)
1	 **2b**	 **5b**	74[a]
2	 **2f**	 **5f**	65[a]
3	 **2h**	 **5h**	62[a]
4	 **2e**	 **6e**	65[b]
5	 **2f**	 **6f**	60[b]

[a] Crude product yield based on the starting diiodoalcohol 2 (see text). [b] Pure product yield based on the starting diiodoalcohol 2.

In conclusion, we have developed a new, rapid and efficient methodology for diiodomethylation of carbonyl compounds starting from SmI_2 and triiodomethane.

Acknowledgement

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