SHORT PAPER

J. Chem. Research (S), 2001, 104–105

A novel one-pot synthesis of cyclopentanol derivatives from aldehydes and α-haloketones by samarium (III) iodide and samarium (II) iodide mediated cascade reactions†

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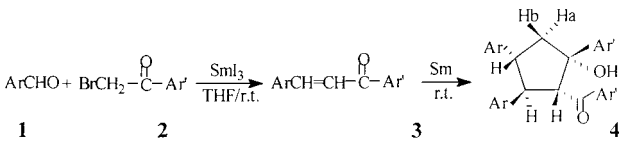
Aldehydes can react with α-haloketones promoted by SmI_3, to give α,β-unsaturated ketones, then, by adding powdered samarium to the reaction mixture, these undergo reductive cyclodimerisation to afford cyclopentanol derivatives under mild conditions

Keywords: samanium iodides, cyclopentanol derivatives

Recently metallic samarium, its salts and organosamarium compounds have been widely employed as useful reagents or catalysts in organic synthesis.[1] Since the pioneering studies by Kagan and co-workers demonstrated the particular effectiveness of samarium diiodide as a mild, neutral, and versatile single electron transfer reductant,[2] the utilisation of SmI_2 in organic synthesis has been well documented. Compared with the application of samarium(II) species in organic synthesis, few applications of samarium(III) species have been reported in organic synthesis.[3] However, the reports, using samarium (III) in organic chemistry have increased recently. We have reported that α-haloketones can react with aldehydes promoted by SMI_3, to give α,β-unsaturated ketones.[4] Sasai reported that 1-chloro-2-heptanone is able to react with benzaldehyde to form α-chloro-β-hydroxy ketones catalysed by $Sm(HMDS)_2$;[5] similarly catalysed by $Sm(OTf)_3$, benzylamine can add to ethyl crotonate to form β-amino esters.[6] Recently, we also reported that α-diketones or α-ketoesters can condense with aldehydes mediated by SmI_3, to form benzylidene-substituted α-diketones or α-ketoesters in fair yields.[7]

As mentioned above, α-haloketones can react with aldehydes to give α,β-unsaturated ketones in the presence of SmI_3 and it was also reported that SmI_2 has been successfully utilised in the reductive cyclodimerisation of α,β-unsaturated ketones to give cyclopentanol derivatives with excellent stereoselectivity.[8,9] These results prompted us to investigate the possibility of a one-pot synthesis of 2-aroyl-1,3,4-triaryl cyclopentanol derivatives (**4**) directly from aryl aldehydes (**1**) and α-haloketones (**2**) through cascade reactions promoted by SmI_3 and SmI_2 without isolating the intermediate – α,β-unsaturated ketones (**3**) from the reaction mixture. Herein we wish to report our preliminary results of this novel one-pot process (Scheme 1).



Scheme 1

When aryl aldehydes (**1**) and α-haloketones (**2**) were treated with 1 equiv. SmI_3 for about 3–4 hours at room temperature, almost all of them were consumed and the corresponding α,β-unsaturated ketones (**3**) were formed. Then, when 0.5 equiv. Sm powder was added to the flask, the colour of the reaction mixture changed from pale yellow into deep-blue gradually, which is the characteristic colour of samarium (II). The samarium (II) generated *in situ* efficiently promoted the reductive cyclodimerisation of the α,β-unsaturated ketones to give 2-aroyl-1,3,4-triaryl cyclopentanol derivatives (4) at room temperature within half an hour. Table 1 summarised the results of the reaction of a number of substrates. The chloro, bromo, alkoxyl groups of the substrates were not reduced under the reaction conditions. The cascade reactions were completed within 4–5 hours at room temperature and afforded the corresponding substituted cyclopentanol in moderate yields. The relative stereochemistry of (**4**) obtained through reductive cyclodimerisation of α,β-unsaturated ketones promoted by SmI_2 and the possible mechanism of such a reductive cyclodimerisation have been established in the literature.[8,9]

Table 1 Reaction of aryl aldehydes and α-haloketones promoted by SmI_3 and SmI_2

Entry	Ar	Ar[1]	Yield/%[a]
1	C_6H_5	C_6H_5	61
2	4-ClC_6H_4	C_6H_5	64
3	2-ClC_6H_4	C_6H_5	58
4	4-$CH_3C_6H_4$	C_6H_5	61
5	3,4-$OCH_2OC_6H_3$	C_6H_5	55
6	3-BrC_6H_4	C_6H_5	58
7	C_6H_5	4-$CH_3C_6H_4$	57
8	3,4-$OCH_2OC_6H_3$	4-$CH_3C_6H_4$	52

[a]Isolated yield of cyclopentanol derivatives.

There are several reports on the synthesis of cyclopentanol derivatives. For example, Paquette *et al.*[10] have reported that *syn*-2-vinylcyclopentanol can be prepared through indium-mediated intramolecular cyclisation of 4′-substituted (*Z*)-and (*E*)-7-bromo-5-heptenophenones; Mikolajczyk *et al.*[11] have reported the preparation of another cyclopentanol derivative, (±)-rosaprostol, an antiulcer drug, in several steps by using

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

dimethyl methanephosphonate as the starting material. Unfortunately, these methods suffered from using expensive reagents and needing substrates with complicated structures. Compared with these reported methods, our results have the advantages of simple operation, one-pot synthesis from accessible substrates, mild conditions and high stereoselectivity.

In conclusion, we have provided a new route to cyclopentanol derivatives, the advantages of which are the accessibility of the starting materials, simple and mild reaction conditions. Further studies to develop other new uses of SmI_3 and SmI_2 promoted cascade reactions are now in progress in our laboratory.

Experimental

General experimental details: Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points were obtained on an electrothermal melting point apparatus and were uncorrected. Infrared spectra were recorded on an Shimadzu IR-408 spectrometer using KBr pellets with absorption maxima indicated in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC-400 (400MHz) spectrometer using $CDCl_3$ solutions. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on a HP 5989B MS spectrometer. Elemental analyses were carried out on a Carlo Erba EA 1110 instrument.

General procedure for the preparation of 2-aroyl-1,3,4-triaryl cyclopentanol derivatives: Under anhydrous conditions, a mixture of powered samarium (0.15g, 1mmol) and iodine (0.375g, 3mmol) in dry THF (20ml) was stirred at room temperature until the samarium disappeared. To the resulting pale yellow suspension of SmI_3 was added simultaneously a α-haloketone (1 mmol) and an aryl aldehyde (1 mmol) and this was stirred until the α-haloketone and aryl aldehyde were almost consumed (monitored by TLC). 0.5 equiv. Sm powder was then added to the flask and the colour of the reaction mixture gradually changed into deep-blue. After the solution was stirred for another half an hour, the colour changed into light green. Then the solution was quenched with dilute HCl (0.1mol/l, 5ml) and extracted with ether (3 × 20ml). The combined extracts were washed with a saturated solution of $Na_2S_2O_3$ (15ml), saturated brine (15ml) and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the crude product was purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1:6) as eluent. All the cyclopentanol products have physical data (m.p.) and spectral characteristics (IR, MS and ^1H NMR) in agreement with the literature data.[9]

1,2-cis-2,3-trans-3,4-trans-2-benzoyl-1,3,4-triphenyl cyclopentanol (**4a**): m.p. 192–193°C (Lit.[9], 192–194°C); ν_{max}/cm^{-1} (KBr) 3440 (OH), 1645 (C=O); δ_H ($CDCl_3$) 2.59 (1 H, dd, *J* 14.4, 6.1, C^5–H_a), 2.98 (1 H, dd, *J* 14.4, 10.7, C^5–H_b), 3.78 (1 H, ddd, *J* 10.7, 10.2, 6.1, C^4–H), 4.10 (1 H, dd, *J* 11.7, 10.2, C^3–H), 4.60 (1 H, d, *J* 11.7, C^2–H), 5.22 (1H, s, OH), 7.01–7.58 (20 H, m, ArH).

1,2-cis-2,3-trans-3,4-trans-2-benzoyl-1-phenyl-3,4-di(4-chlorophenyl) cyclopentanol (**4b**): m.p. 191–193°C (Lit.[9] 192–194°C); ν_{max}/cm^{-1} (KBr) 3445 (OH), 1640 (C=O); δ_H ($CDCl_3$) 2.52 (1 H, dd, *J* 14.4, 6.1, C^5–H_a), 3.01 (1 H, dd, *J* 14.4, 10.7, C^5–H_b), 3.70 (1 H, ddd, *J* 10.7, 10.1, 6.1, C^4–H), 4.05 (1 H, dd, *J* 11.7, 10.1, C^3–H), 4.53 (1 H, d, *J* 11.7, C^2–H), 5.10 (1H, s, OH), 6.95–7.78 (18 H, m, ArH).

1,2-cis-2,3-trans-3,4-trans-2-benzoyl-1-phenyl-3,4-di(2-chlorophenyl) cyclopentanol (**4c**): m.p. 191–192°C (Lit.[9] 192–193°C), ν_{max}/cm^{-1} (KBr) 3445 (OH), 1645 (C=O); δ_H ($CDCl_3$) 2.38 (1 H, dd, *J* 14.4, 5.1, C^5–H_a), 3.10 (1 H, dd, *J* 14.4, 10.7, C^5–H_b), 4.68–4.82 (3 H, m, C^4–H, C^3–H, C^2–H)), 5.62 (1H, s, OH), 7.01–8.15 (18 H, m, ArH).

1,2-cis-2,3-trans-3,4-trans-2-benzoyl-1-phenyl-3,4-di(4-methylphenyl) cyclopentanol (**4d**): m.p. 186–187°C (Lit.[9] 188–190°C); ν_{max}/cm^{-1} (KBr) 3440 (OH), 1640 (C=O); δ_H ($CDCl_3$) 2.18 (3 H, s, CH_3), 2,30 (3 H, s, CH_3), 2.54 (1 H, dd, *J* 14.4, 6.3, C^5–H_a), 3.01 (1 H, dd, *J* 14.4, 10.7, C^5–H_b), 3.70 (1 H, ddd, *J* 10.7, 10.2, 6.6, C^4–H), 4.15 (1 H, dd, *J* 11.7, 10.2, C^3–H), 4.52 (1H, *d*, *J*, 11.7, C^2–H), 5.24 (1H, s, OH), 6.87–7.63 (18 H, m, ArH).

1,2-cis-2,3-trans-3,4-trans-2-benzoyl-1-phenyl-3,4-di(3,4-methylenedioxyl-phenyl) cyclopentanol (**4e**): m.p. 181–183°C (Lit.[9] 183–184°C); ν_{max}/cm^{-1} (KBr) 3460 (OH), 1645 (C=O); δ_H ($CDCl_3$) 2.56 (1 H, dd, *J* 14.4, 6.1, C^5–H_a), 2.99 (1 H, dd, *J* 14.4, 10.6, C^5–H_b), 3.72 (1 H, ddd, *J* 10.6, 10.0, 6.1, C^4–H), 4.07 (1H, dd, *J* 11.6, 10.1, C^3–H), 4.43 (1H, d, *J* 11.5, C^2–H), 5.23 (1H, s, OH), 5.76 (2 H, s, OCH_2O), 5.88 (2H, s, OCH_2O), 6.61–7.63 (16 H, m, ArH).

1,2-cis-2,3-trans-3,4-trans-2-benzoyl-1-phenyl-3,4-di(3-bromophenyl) cyclopentanol (**4f**): m.p. 170–172°C ν_{max}/cm^{-1} (KBr) 3445 (OH), 1650 (C=O); δ_H ($CDCl_3$) 2.56 (1H, dd, *J* 14.4, 6.1, C^5–H_a), 2.96 (1 H, dd, *J* 14.4, 10.7, C^5–H_b), 3.68 (1H, ddd, *J* 10.7, 10.1, 6.1, C^4–H), 4.05 (1 H, dd, *J* 11.7, 10.2, C^3–H), 4.57 (1 H, d, *J* 11.7, C^2–H), 5.19 (1H, s, OH), 7.12–7.68 (18 H, m, ArH). *m/z* 576 (M^+, 0.4), 456 (5), 287 (10), 289 (9), 105 (100), 77(27); (Found: C, 62.31; H, 4.03, $C_{30}H_{24}Br_2O_2$, requires C, 62.50; H, 4.17%).

1,2-cis-2,3-trans-3,4-trans-2-(-4-methylbenzoyl)-1-(4-methylphenyl)-3,4-diphenyl cyclopentanol (**4g**): m.p. 169–170°C (Lit.[9] 170–171.5°C); ν_{max}/cm^{-1} (KBr) 3450 (OH), 1640 (C=O); δ_H ($CDCl_3$) 2.25 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.61 (1 H, dd, *J* 14.4, 6.1, C^5-H_a), 2.94 (1 H, dd, *J* 14.4, 10.6, C^5–H_b), 3.76 (1 H, ddd, *J* 10.6, 9.5, 6.1, C^4–H), 4.09 (1 H, dd, *J* 11.6, 9.6, C^3-H), 4.52 (1 H, d, *J* 11.6, C^2–H), 5.25 (1H, s, OH), 6.92–7.80 (18 H, m, ArH).

1,2-cis-2,3-trans-3,4-trans-2-(4-methylbenzoyl)-1-(4-methylphenyl)-3,4-di(3,4-methylenedioxyphenyl) cyclopentanol (**4h**): m.p. 170–172°C (Lit.[9] 171–172°C); ν_{max}/cm^{-1} (KBr) 3440 (OH), 1640 (C=O); δ_H ($CDCl_3$) 2.24 (3 H,s, CH_3), 2.47 (1 H, dd, *J* 14.4, 6.1, C^5–H_a), 3.00 (1 H, dd, *J* 14.4, 10.7, C^5–H_b), 3.67 (1 H, ddd, *J* 10.7, 10.1, 6.1, C^4-H), 4.01 (1 H, dd, *J* 11.7, 10.1, C^3–H), 4.40 (1 H, d, *J* 11.7, C^2-H), 5.22 (1H, s, OH), 5.78 (2 H, s, OCH_2O), 5.84 (2 H, s, OCH_2O), 6.55–7.52 (14 H, m, ArH).

We thank the National Natural Science Foundation of P.R. China (No.20072033) and NSF of Zhejiang Province for financial support.

Received 18 December 2000, accepted 18 January 2001
Paper 00/664

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