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Cyclopropane ring formation by an SmI_2 mediated cyclisation of δ-halo-α,β-unsaturated esters

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Abstract

δ-Iodo- and δ-bromo-α,β-unsaturated esters with various substituents at the β- and γ-positions readily cyclise to cyclopropane compounds in the presence of samarium diiodide and a proton source. © 1999 Elsevier Science Ltd. All rights reserved.

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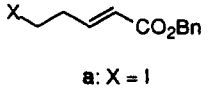
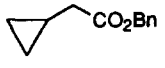
Since the seminal report by Kagan and co-workers,[1] SmI_2 has found many applications in synthetic organic chemistry. In particular, SmI_2-mediated sequenced radical–anionic or anionic–radical reactions are of great interest for the synthesis of various carbocyclic and heterocyclic molecules, as amply demonstrated especially by Molander and co-workers.[2] Up to now, these reactions have been essentially used for the obtention of five- or six-membered rings. For instance, Molander and Harris recently described the SmI_2-induced cyclisation of ζ- and η-iodo-α,β-unsaturated esters to 1-carbalkoxyalkyl-substituted cyclopentane or cyclohexane derivatives.[3] In the present communication, we report that δ-iodo- and δ-bromo-α,β-unsaturated esters also cyclise in the presence of SmI_2, leading to cyclopropane compounds.[4]



a: X = I
b: X = Br
c: X = H

1



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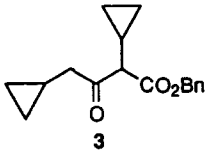

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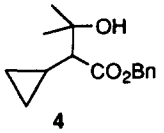

4

In a first experiment, we found that benzyl 5-iodopent-2-enoate **1a** reacted with SmI_2 (2.5 equiv. as a 0.1 M solution in THF) in the presence of HMPA (4 equiv.) within 5 min at room temperature to give,

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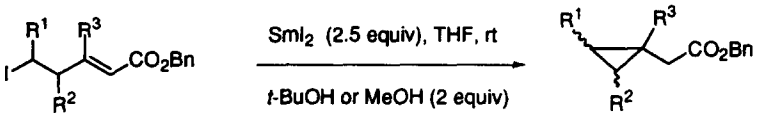
Table 1
SmI_2-mediated cyclisation of δ-iodo-α,β-unsaturated esters



Entry	R^1	R^2	R^3	Yield[a] (%) in cyclised product	Diastereoisomeric composition[b]
1	H	H	H	99	-
2	Me	"	"	87	40/60
3	H	Me	"	82	40/60
4	"	O-CH_2-CH=CH_2	"	87	45/55
5	Me	Me	"	81	35/65[c]
6[d]	Ph	H	"	81	58/42
7[d]	"	Me	"	77	75/20/5[e]
8[f]	H	H	Me	80	-

[a] Yields refer to pure chromatographed products. [b] *cis/trans* ratio unless otherwise specified. [c] Only two of the three possible stereomers were detected, the first one with Me substituents *trans* to each other, the second one with both Me substituents *trans* to the carbobenzyloxymethyl group. [d] The methyl ester, instead of the benzyl ester was used as starting material. [e] Only three of the four possible stereomers were detected but NMR analysis of the mixture did not allow to attribute with certainty their respective structures. [f] The reaction was run in the presence of 2 equiv. of HMPA.

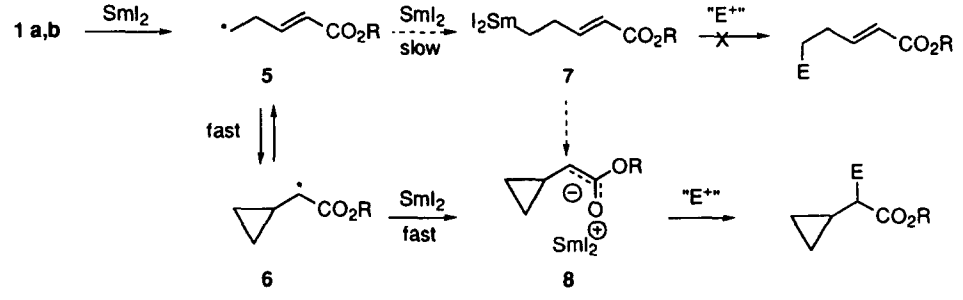
after quenching with H_2O, a ca. 1:1 mixture (as determined by NMR) of benzylcyclopropylacetate **2** and benzyl 2,4-dicyclopropyl-3-oxobutanoate **3** in 87% overall yield. Benzyl alcohol was also formed in the reaction. When the reaction was repeated in the presence of a proton source (benzyl alcohol or *tert*-butyl alcohol, 2 to 3 equiv.), benzylcyclopropylacetate was this time selectively obtained in 99% yield, both from the iodo-compound **1a** and its bromo-analogue **1b**. No uncyclised reduction product **1c** could be detected. The reactions were also run in the presence of acetone instead of a proton source, in which case the cetolisation product **4** was obtained in 45–65% yield, together with benzylcyclopropylacetate **2**. Finally, we noted that, in the absence of HMPA, all the reactions described above gave similar results but required a longer time, especially for bromides (1 h for **1b** for instance).

To roughly delineate the scope of these SmI_2-mediated cyclisations, we next studied the reactivity of a series of δ-bromo- and δ-iodo-α,β-unsaturated esters with various substituent patterns. In all cases, the reactions were allowed to proceed for 3 h at room temperature, using 2.5 equiv. of SmI_2, in THF without HMPA and in the presence of *t*-BuOH or MeOH (2 equiv.) as the proton source. The products of reaction were thoroughly characterised by IR and NMR spectroscopy and by GC/MS analysis after chromatographic purification. The results of this study concerning δ-iodo-α,β-unsaturated esters are summarised in Table 1. Very similar results were obtained with the bromo-analogues.

These preliminary results seem to indicate that the presence of substituents at the γ- or δ-position (entries 2–4 and 6) or at *both* the γ- and δ-positions (entries 5 and 7) does not alter the course of the reaction. In all cases, the conversion of starting material was complete and the products of reductive cyclisation were obtained as a mixture of stereoisomers. These stereoisomers, usually clearly detectable by GC/MS analysis and by the characteristic NMR ABX systems displayed by the methylenic protons α to the carbobenzyloxy group, could unfortunately not be separated by column chromatography. In neither of these cases could other reduction products be detected in the crude reaction mixture. Finally,

the compound in entry 8, bearing a methyl group at the β-position of the double bond, was also found to cyclise but at a slower rate and HMPA was added to the medium to accelerate the process. To the best of our knowledge, such metal-induced 3-*exo*-trig cyclisation reactions of δ-halo-α,β-unsaturated keto-compounds, that probably involve radical intermediates (vide infra), are unprecedented in the literature, except for an isolated example of a chromous acetate mediated reaction described in the steroid series more than 30 years ago by Barton et al.[5]

At the present state of our investigations, no definite conclusions can be drawn concerning the mechanism of these cyclisation reactions. A radical–anionic sequence, similar to the one convincingly proposed by Molander and Harris for the SmI_2-mediated cyclisation of ζ- or η-iodo-α,β-unsaturated esters or amides[3] may be considered. Following these authors, alternative mechanisms involving the formation of anionic species (i.e. either an organosamarium species formed at the carbon–iodide bond or a metal radical enolate species arising from SmI_2 reduction of the enoate moiety) before the cyclisation step may seem unlikely, since the reactions are carried out directly in the presence of a proton source. Furthermore, as already pointed out by Molander and Harris in related cases,[3] the formation of the organosamarium derivative of the alkoxysubstituted compound (entry 4) should probably have been followed by a rapid β-elimination of the vicinal alkoxy group, thus leading to diene. The radical anionic sequence, as applied to the simplest case of unsubstituted compounds **1a,b**, is represented in Scheme 1: the δ-halo-α,β-unsaturated ester by monoelectronic reduction by a first molecule of SmI_2 leads to the homoallyl radical **5**, which may then rapidly cyclise to α-carbalkoxy-substituted cyclopropylmethyl radical **6** according to the 3-*exo*-trig mode.[6] In most cases, and owing to ring strain, cyclopropylmethyl radicals are thermodynamically much disfavoured[7] in comparison with their corresponding open homoallylic forms and, compared to 5-*exo*-trig processes which are extensively used in organic synthesis,[8] examples of radical 3-*exo*-trig processes leading to cyclopropane compounds are very few and always involve molecules with very specific structural features.[9] In our reactions, however, and despite the unfavourable thermodynamic bias,[10] the electrophilic α-carbalkoxy-substituted radical **6** would be rapidly reduced by a second molecule of SmI_2 to the corresponding samarium enolate **8** thus allowing the displacement of the overall reaction towards cyclisation. Trapping of **8** by the electrophilic quencher (H^+, acetone) would complete the reaction. In the absence of suitable electrophilic species, Claisen condensation would occur, as exemplified by the aforementioned conversion of **1a** to β-ketoester **3**.



Scheme 1.

If the radical anionic sequence exposed above reasonably accounts for the cyclisation observed in entries 1–5 and 8, the fact that the cyclisation *also* takes place with substrates having a phenyl substituent at the δ-position (entries 6 and 7) is puzzling to us since the stabilising effect of the phenyl ring should make the cyclisation of the corresponding homoallyl radicals much more difficult and, on the contrary, facilitates the reverse ring-opening process. Indeed, the ring opening of a cyclopropylmethyl radical

bearing a phenyl substituent on the ring is among the fastest radical reactions calibrated to date,[11] with $k_{-c}=3\times10^{11}$ s^{-1} at 25°C. Despite the difficulties previously mentioned (vide supra), we therefore think that the possibility of an anionic cyclisation process cannot be definitely ruled out, at least for the δ-phenyl-substituted compounds of entries 6 and 7.

We are currently applying the SmI_2-mediated cyclisation of δ-halogeno-α,β-unsaturated esters, nitriles and amides to synthetically useful transformations. Experiments aiming at a better understanding of the mechanism of this reaction are also under way.

Acknowledgements

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6. The reduction of radical **5** to the organosamarium(II) species **7** is very likely to be too slow a process to *kinetically* compete with the very fast (see Ref. 8) radical ring closing process leading from **5** to **6**. Competition between (slower) radical cyclisation of primary radicals onto unsubstituted terminal double bond according to the 5-*exo*-trig mode and their trapping by SmI_2 in THF has been studied by Curran and co-worker (Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717–1720). Rate constant values ranging from 5×10^5 to 7×10^6 M^{-1} s^{-1} in dependence of the amount of HMPA present in the medium, for the reduction of primary alkyl radicals by SmI_2 could thus be determined.
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the two radical species much in favour of the homoallylic one. For the sake of comparison, we also studied the reaction of iodide **1a** with 1 equiv. of Bu_3SnH at an initial concentration of 0.02 M in benzene at reflux and in the presence of AIBN. Under these conditions, and in contrast to what was observed in the SmI_2-mediated reaction, the uncyclised direct reduction product **1c** was selectively obtained. Since the equilibration between **5** and **6** is fast compared to hydrogen abstraction from tributyltin hydride and since, due to transition state polarisation effect, the presence of a carbalkoxy substituent does not appreciably change the rate of hydrogen abstraction from tributyltin hydride by alkyl radicals (Newcomb, M.; Horner, J. H.; Filipowski, M. A.; Ha, C.; Park, S.-U. *J. Am. Chem. Soc.* **1995**, *117*, 3674–3684), these preliminary observations, which would need further more detailed analysis, seem to indicate that the equilibrium between **5** and **6** is largely in favour of **5**.

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