Pergamon

Tetrahedron Letters 39 (1998) 2115–2118

TETRAHEDRON LETTERS

Reductive Opening of Cyclopropylogous α-Hydroxy Aldehydes and Ketones by Samarium(II) Iodide

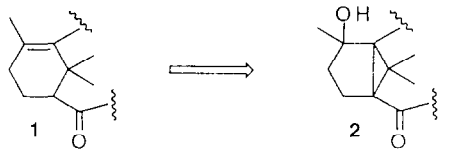
Alex Nivlet,[a] Valérie Le Guen,[a] Luc Dechoux,[a,‡] Thierry Le Gall,[a,*] Charles Mioskowski[a,b,*]

[a]CEA-Saclay, Service des Molécules Marquées, Bât. 547, Département de Biologie Cellulaire et Moléculaire, F-91191 Gif-sur-Yvette, France
[b]Faculté de Pharmacie, Université Louis Pasteur, Laboratoire de Synthèse Bio-Organique associé au CNRS, 4 route du Rhin, BP 24, F-67401 Illkirch, France

Received 2 December 1997; accepted 1 January 1998

Abstract: The regioselectivity of the reductive opening of cyclopropylogous α-hydroxy carbonyl compounds using SmI_2 in THF or THF-HMPA was studied and shown to depend strongly on the substrate. In some cases, a tandem cyclopropyl opening-deoxygenation reaction afforded the corresponding γ-keto alkenes in one step.

In the course of a study on the synthesis of taxanes, we wanted to generate a structure of the type **1** from a bicyclic system **2**, by a process involving the regioselective breaking of a carbon-carbon bond of the cyclopropane ring and the elimination of the tertiary hydroxyl group to establish the double bond of the cyclohexene ring (Scheme 1).



Scheme 1

Various conditions have been reported to cleave the cyclopropane ring of cyclopropyl ketones. Lithium in liquid ammonia,[1] catalytic hydrogenation,[2] tributyltin hydride,[3] photochemical hydrogen transfer[4] and samarium(II) iodide[5] have been used for that purpose.

In the context of taxanes synthesis, three reports describe the access to models of the bicyclic [A,B] system that make use of the cleavage of a cyclopropyl ring (which in these examples was not substituted by the two methyl groups), under oxydative,[6] acidic,[7] and photochemical condition.[8]

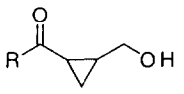
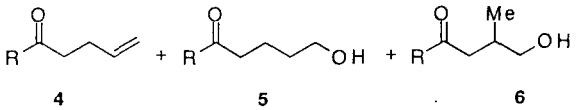
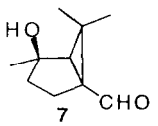
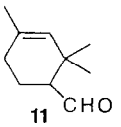
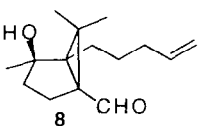
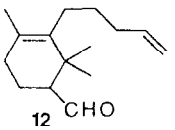
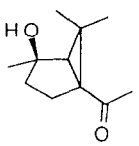
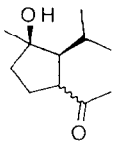
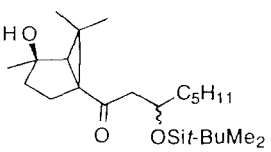
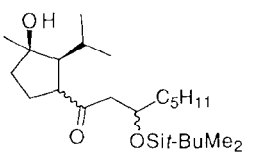
The reductive opening of cyclopropylogous α-haloketones by treatment with SmI_2 has been described.[9] Moreover, it is well known that SmI_2 also efficiently deoxygenates α-hydroxy ketones,[10] and thus seemed the more convenient reagent to employ in our study. In this communication, we report the samarium(II) iodide-mediated ring opening of cyclopropylogous α-hydroxy carbonyl compounds.

*Fax: 01 69 08 79 91; e-mail: legall@dsvidf.cea.fr
*Fax: 03 88 67 88 91; e-mail: mioskow@aspirine.u-strasbg.fr

0040-4039/98/$19.00
PII: S0040-4039(98)00063-X

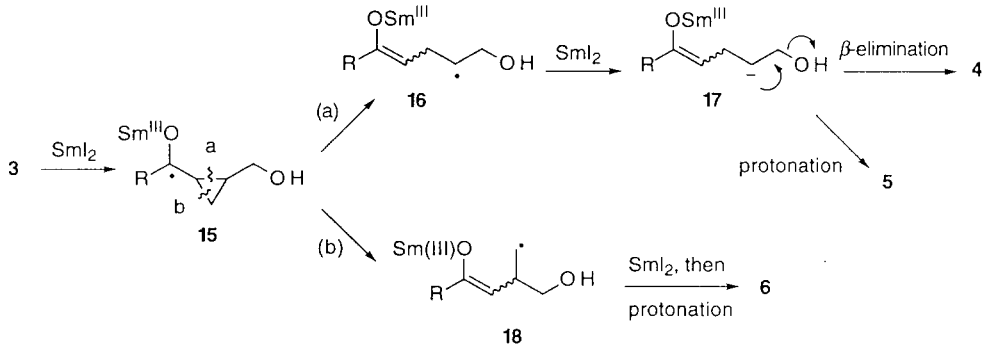
Two types of substrates were used: compounds **3a-c**,[11] which are *cis*-substituted (*de* > 90%) and do not have a *gem*-dimethyl moiety, and compounds **7-10**, that contain a bicyclo[3.1.0] system ring. The results of the opening reactions are presented in the Table. They were performed in THF at room temperature, but when ketones were used as substrates (entries 1,2,3,6,7), it was necessary to add HMPA (8-10 equivalents) as a co-solvent.[12]

Table : Reaction of Cyclopropylogous α-Hydroxy Carbonyl Compounds with SmI_2 in THF or THF-HMPA

Entry	Reactant[a]	Products (yields)
	 **3**	 **4** + **5** + **6**
1	**3a** (R = cyclohexyl)	**4a** (76%)
2	**3b** (R = $(CH_2)_8CH_3$)	**4b** (53%) + **5b** (13%)+ **6b** (20%)
3	**3c** (R = $(CH_2)_2Ph$)	**4c** (47%) + **5c** (15%)+ **6c** (31%)
4	 **7**	 **11** (60%)
5	 **8**	 **12** (51%)
6	 **9**	 **13** (2 diastereomers: 70 / 30) (68%)
7	 **10** (2 diastereomers: 55 / 45)	 **14** (4 diastereomers: 38 / 32 / 17 / 13) (80%)

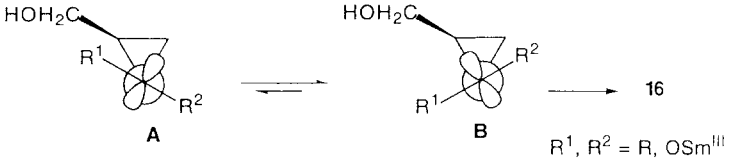
[a] Solvent: THF-HMPA (entries 1,2,3,6,7); THF (entries 4,5).

The reaction of ketones **3** led to mixtures of homoallylic ketones **4**, δ-hydroxy ketones **5** and α-methyl γ-hydroxy ketones **6** in variable amounts (entries 1,2,3). A suggested mechanism to account for these results (scheme 2) invokes the formation of ketyl radical **15**, which rearranges to either radical **16** (pathway a) or **18** (pathway b). A second equivalent of SmI_2 reduces this radical to the anion **17**, which undergoes a β-elimination of hydroxide, thus affording compound **4**. Alternatively, protonation of **17** may lead to alcohol **5**, while radical **18** is converted to alcohol **6**.



Scheme 2

The observed regioselectivity is in good agreement with earlier studies by Davies and Pereyre[13] concerning the opening of *cis*-2-methylcyclopropylcarbinyl radicals: of the two conformers **A** and **B** in which the singly occupied *p*-orbital and one of the cyclopropane C-C bond overlap, conformer **A** is unfavored because of a strong interaction between the hydroxymethyl and R^1 groups. Conformer **B** eventually leads to the radical **16** (Scheme 3).



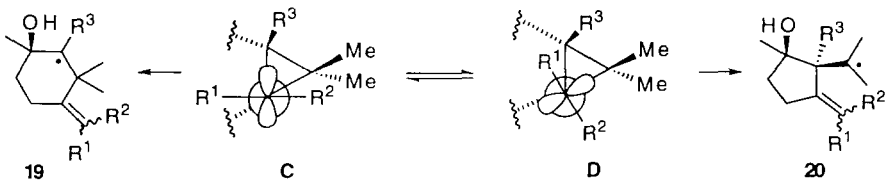
Scheme 3

The reactions of bicyclic compounds **7-10** with samarium(II) iodide proceed with a regioselectivity that depends on the carbonyl group in the substrate, since aldehydes **7** and **8** lead to cyclohexenes **11** and **12**, respectively, while ketones **9** and **10** lead to cyclopentanols **13** and **14**, which were obtained as mixtures of diastereomers (entries 4-7).

Two factors must be taken into account to explain these results: 1) In the first step of all these reactions, the ketyl radical generated is *cis* to one of the methyl groups, thus a disfavorable interaction may occur, as in the former examples. 2) In the absence of such steric interaction, the C-C bond which will be broken is likely to be the less substituted, according to several earlier works; this has been explained by Mariano and Bay using the Frontier Molecular Orbitals theory.[14]

Thus, ketyl radicals generated from the ketones **9** and **10** rearrange according to conformer **D** to give the radical **20**, because of the strong interaction between R^2 and the *cis*-methyl group in the conformer **C** (Scheme 4). This interaction can be avoided in the reactions of aldehydes (in the conformer where R^2 = H); thus, in the

case of aldehyde **7** (R^3 = H), the less substituted C-C bond breaks to generate the radical **19**. The same bond is also cleaved in the reaction of aldehyde **8** although it is more substituted in that case ($R^3 = C_5H_9$).



R^1, R^2 = H or alkyl, OSm^{III}; R^3 = H or alkyl

Scheme 4

In conclusion, we have shown that samarium(II) iodide mediates the ring opening of cyclopropylogous α-hydroxy carbonyl compounds. The regioselectivity of the opening is strongly dependant of the substrate. In several cases, a tandem cyclopropyl opening-deoxygenation reaction was observed, producing the corresponding γ-keto alkenes in fair to good yields. This pathway may be of synthetic value in the access to taxanes.

‡ Current address: Laboratoire de Synthèse Asymétrique, Université Pierre et Marie Curie, 4 place Jussieu, 75005 Paris.

References and Notes

1. a) Norin, T. *Acta Chem. Scand.* **1965**, *19*, 1289-1292; b) Dauben, W. G.; Deviny, E. J. *J. Org. Chem.* **1966**, *31*, 3794-3798; c) Dauben, W. G.; Wolf, R. E. *J. Org. Chem.* **1970**, *35*, 374-379; d) Fraisse-Jullien, R.; Frejaville, C. *Bull. Soc. Chim. Fr.* **1968**, 4449-4455.
2. Fraisse-Jullien, R.; Frejaville, C.; Toure, V.; Derieux, M. *Bull. Soc. Chim. Fr.* **1968**, 4444-4449.
3. a) Pereyre, M.; Godet, J.-Y. *Tetrahedron Lett.* **1970**, 3653-3656; b) Davies, A. G.; Godet, J.-Y.; Muggleton, B.; Pereyre, M. *J. Chem. Soc., Chem. Commun.* **1976**, 813-814; c) Davies, A. G.; Muggleton, B.; Godet, J.-Y.; Pereyre, M.; Pommier, J.-C. *J. Chem. Soc., Perkin II* **1976**, 1719-1724; d) Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. Chem. Soc., Perkin II* **1979**, 589-592.
4. a) Cossy, J.; Aclinou, P., Bellosta,V.; Furet, N.; Baranne-Lafont, J.; Sparfel, D.; Souchaud, C. *Tetrahedron Lett.* **1991**, *32*, 1315-1316; b) Cossy, J.; Furet, N.; BouzBouz, S. *Tetrahedron* **1995**, *51*, 11751-11764; c) Kirschberg, T.; Mattay, J. *Tetrahedron Lett.* **1994**, *35*, 7217-7220; d) Kirschberg, T.; Mattay, J. *J. Org. Chem.* **1996**, *61*, 8885-8896.
5. a) Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, *32*, 6211-6214; b) Hwang, J.-T.; Liao, C.-C. *Tetrahedron Lett.* **1991**, *32*, 6583-6586.
6. Kumar, P.; Rao, A. T.; Saravanan, Pandey, B. *Tetrahedron Lett.* **1995**, *36*, 3397-3400.
7. Thielemann, W.; Schäfer, H. J.; Kotila, S. *Tetrahedron* **1995**, *51*,12027-12034.
8. Cossy, J.; BouzBouz, S. *Tetrahedron Lett.* **1997**, *38*, 1931-1932.
9. Beerli, R.; Brunner, E. J.; Borschberg, H.-J. *Tetrahedron Lett.* **1992**, *33*, 6449-6452.
10. Recent review on the use of SmI_2: Molander, G.; A. *Organic Reactions* **1994**, *46*, 211-367.
11. Dechoux, L.; Ebel, M.; Jung, L.; Stambach, J. F. *Tetrahedron Lett.* **1993**, *34*, 7405-7408.
12. For a discussion on the role of HMPA in SmI_2-mediated reductions, see: Molander, G. A; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132.
13. Blum, P.; Davies, A. G.; Pereyre, M.; Ratier, M. *J. Chem. Soc., Chem. Commun.* **1976**, 814-816.
14. Mariano, P. S.; Bay, E. *J. Org. Chem.* **1980**, *45*, 1763-1769.