Tetrahedron Letters, Vol.32, No.43, pp 6211-6214, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

SAMARIUM(II) IODIDE PROMOTED RADICAL RING OPENING REACTIONS OF CYCLOPROPYL KETONES

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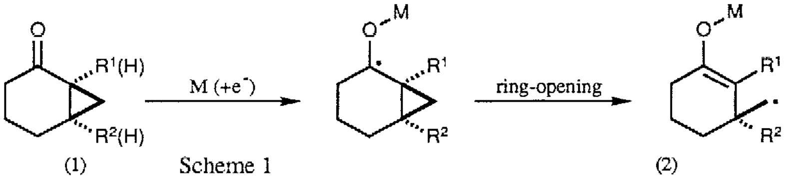
Key Words: Samarium(II) Iodide Reduction; Cyclopropylcarbinyl Radical Rearrangement; Cyclopropyl Ketone; Radical Cyclisation; Samarium Enolate.

Abstract: *Radical ring opening reactions of cyclopropyl ketones mediated by samarium(II) iodide-induced single electron transfer have permitted the elaboration of a tandem rearrangement cyclisation strategy. The resultant samarium enolates may be effectively quenched on oxygen or carbon by electrophiles.*

Although a vast array of preparatively useful free radical reactions have been used in organic synthesis in the past decade, the necessity for processes which lead to concomitant incorporation or retention of useful functionality for further manipulation has been increasingly recognised in recent years.[1]

As part of our interest in the development of useful sequences featuring the cyclopropylcarbinyl homoallylic radical rearrangement,[2] and with the above concept in mind, we elected to examine the single electron transfer induced ring opening reactions of cyclopropyl ketones (**1**), as outlined in Scheme 1.



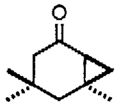
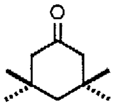
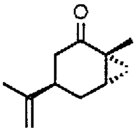
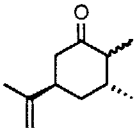
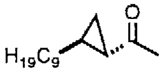
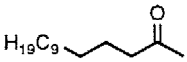
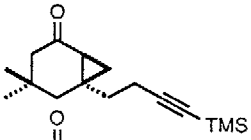
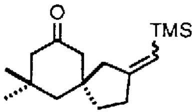
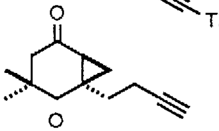
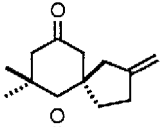
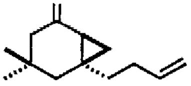
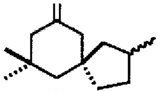
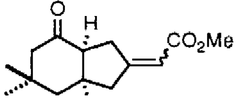
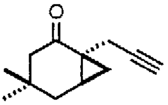
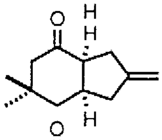
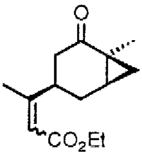
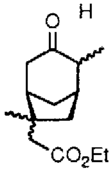
Scheme 1

We were particularly attracted by the inherent synthetic potential of intermediate (**2**), which results from stereochemically controlled[3,2] ring opening of the exocyclic cyclopropyl carbon-carbon bond in a bicyclic system. Thus, in the first instance (but subject, of course, to the nature of metal M), formation of a regiospecific enolate provides obvious opportunities for subsequent reaction with electrophiles. Of equal import, however, the generation of the new carbon-centred radical in (**2**) offers possibilities not only for simple hydrogen atom abstraction from solvent, but also for further controlled intramolecular carbon-carbon bond formation by judicious introduction of a pendant chain possessing an unsaturated radicophilic acceptor.

Although many examples of radical additions and electron transfer reactions to cyclopropyl ketones have been documented,[4] the formation of strongly basic dianions by further electron transfer or hydrolysis has, in many cases, effectively precluded both the operation of free radical chemistry and controlled enolate reactions. The overall utility of such a sequence has consequently been undervalued.

As part of a more extensive study,[5] we now report that samarium(II) iodide[6]/tetrahydrofuran/DMPU[7] is an effective reagent which fulfills the necessary criteria for efficient generation of intermediates (**2**). Indeed, during the course of our own work, a single example of a spirocyclic cyclopropyl ketone cleavage using samarium(II) iodide in the presence of an iron(III) catalyst has been described.[8] The reaction conditions reported by these

Table 1: Reaction of Cyclopropyl Ketones with Samarium(II) Iodide / THF / DMPU

Entry	Reactant Ketone	Product Ketone	Yield
1			39%
2			34%*
3			49%
4			79%†
5			57%
6			36%*
7			77%†
8			36%
9			45%*

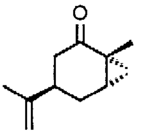
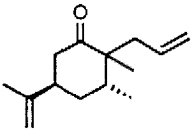
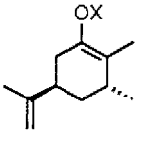
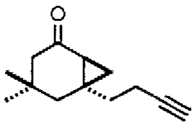
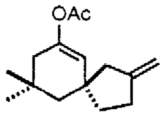
* Isolated as a mixture of diastereomers
† Isolated as a mixture of geometric isomers

authors, however, involving hydrogen atom abstraction from solvent and protic media, effectively prevented full exploitation of the system in terms of further carbon-carbon bond formation.

The preliminary results for a variety of readily assembled substrates involving dropwise addition of samarium(II) iodide to a solution of the ketone in tetrahydrofuran - DMPU (9:1) followed by hydrolytic work up[9] are given in Table 1. Initially, we chose to examine the simpler bicyclo[4.1.0] derivatives (entries 1 and 2) which proceeded with the anticipated[2,3,4] kinetic regioselectivity under stereoelectronic control. In sharp contrast, however, the *trans*-disposed monocyclic system (entry 3) afforded the linear methyl ketone as the sole *regioisomer to be isolated. This result is clearly of interest for further study; it differs markedly from* those obtained on similar *trans*-cyclopropyl ketones using such varied systems as lithium-ammonia,[10] neat tributylstannane[11] and zinc-chlorotrimethylsilane.[5] Entries 4 - 9 illustrate the potential, through differing connective placement of a radical accepting chain, for a tandem rearrangement - 5-*exo* protocol which may be used to generate a variety of linearly fused, spirocyclic or bridged bicyclic structures, even with relatively unactivated traps.

Since the overall process should also result in some form of samarium enolate, it was also of considerable interest to examine whether such species could be effectively quenched or used for further *in situ* carbon-carbon bond formation. In this respect, it is pertinent to note a recent observation by Curran in which a samarium enolate was trapped by an aldehyde to give a product derived by aldolisation and subsequent Tischenko reaction.[12] Examination of the results in Table 2 reveals that direct formation of both enolic derivatives and carbon alkylated products is possible under the reaction conditions. Comparisons with the yields in Table 1 suggests that these reactions approach those of simple hydrolysis in terms of overall efficiency.[13] Moreover, the examples cited indicate that both tri- and tetrasubstituted samarium enolates can be usefully employed.

Table 2: Trapping of Intermediate Samarium Enolates with Electrophiles

Reactant Ketone	Electrophile	Product	Yield
			37%*
	TMSCl† TBDMSOTf† AcCl		X=TMS, 34% X=TBDMS, 20% X=Ac, 33%
	AcCl		57%§

* Stereochemistry α to the carbonyl group has yet to be established

† 2,6-Lutidine was also added in these cases

§ *n.O.e. experiments confirmed the enol-acetate geometry*

In summary, the present tandem rearrangement cyclisation strategy using cyclopropyl ketone substrates is made possible by virtue of the unique properties of samarium(II) iodide, which fulfills a dual rôle in this instance, acting as a clean one electron reducing agent and generating useful metal enolates.

We thank SERC and Quest International for the provision of a CASE studentship.

References and Notes.

1. D.P. Curran, *Synthesis*, 1988, 417 and 489; G. Pattenden, *Chem. Soc. Rev.*, 1988, **17**, 361; B. Giese, "Radicals in Organic Synthesis: formation of C-C bonds", Pergamon Press, Oxford, 1986.
2. J.D. Harling, W.B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1988, 1380; M.C.M. de C. Alpoim, A.D. Morris, W.B. Motherwell, D.M. O'Shea, *Tetrahedron Lett.*, 1988, **29**, 4173.
3. S.J. Cristol, R.V. Barbour, *J. Am. Chem. Soc.*, 1968, **90**, 2832; E.C. Friedrich, R.L. Holmstead, *J. Org. Chem.*, 1972, **37**, 2546 and 2550; A.L.J. Beckwith, G. Phillipou, *Aust. J. Chem.*, 1976, **29**, 123; D.L.J. Clive, S. Daigneault, *J. Org. Chem.*, 1991, **56**, 3801.
4. T. Norin, *Acta Chem. Scand.*, 1965, **19**, 1289; W.G. Dauben, E.J. Deviny, *J. Org. Chem.*, 1966, **31**, 3794; W.G. Dauben, L. Schutte, R.E. Wolf, E.J. Deviny, *J. Org. Chem.*, 1969, **34**, 2512; J. Cossy, P. Aclinou, V. Bellosta, N. Furet, J. Baranne-Lafont, D. Sparfel, C. Souchard, *Tetrahedron Lett.*, 1991, **32**, 1315; M. Pereyre, J.-Y. Godet, *Tetrahedron Lett.*, 1970, 3653; M. Degueil-Castaing, A. Rahm, N. Dahan, *J. Org. Chem.*, 1986, **51**, 1672; K.J. Kulicke, B. Giese, *Synlett*, 1990, 91.
5. R.A. Batey, J.D. Harling, W.B. Motherwell, paper in preparation.
6. P. Girard, J.L. Namy, H.B. Kagan, *J. Am. Chem. Soc.*, 1980, **102**, 2693; J.A. Soderquist, *Aldrichimica Acta*, 1991, **24**, 15; H.B. Kagan, *New J. Chem.*, 1990, **14**, 453; H.B. Kagan, J.L. Namy, *Tetrahedron*, 1986, **42**, 6573.
7. T. Mukhopadhyay, D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 385; T.L. Fevig, R.L. Elliott, D.P. Curran, *J. Am. Chem. Soc.*, 1988, **110**, 5064. DMPU is 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.
8. G.A. Molander, J.A. McKie, *J. Org. Chem.*, 1991, **56**, 4112.
9. Typical procedure for the samarium(II) iodide reactions (unoptimised): To a solution of cyclopropyl ketone (0.5 mmol), in THF/DMPU (9:1, 8.0 ml) was added dropwise a solution of samarium(II) iodide (0.1M in THF) at room temperature under Ar, until the purple coloration persisted. After 5 mins, the reaction mixture was quenched with $NaHCO_3$ (sat. aq.). The aqueous layer was extracted with ether (3x25ml), and the combined organics washed with water (20ml), brine (20ml), dried/$MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by silica gel chromatography. In the case of the trapping experiments, after the end-point was reached, the reaction mixture was cooled to -78°C, and an excess of the electrophile added. After stirring for 30 min, the reaction mixture was allowed to warm slowly to room temperature, stirred for a further 30-60 mins and quenched in the usual way.
10. W.G. Dauben, R.E. Wolf, *J. Org. Chem.*, 1970, **35**, 374.
11. A.G. Davies, J.-Y. Godet, B. Muggleton, M. Pereyre, *J. Chem. Soc., Chem. Commun.*, 1976, 813; M. Pereyre, J.-P. Quintard, *Pure Appl. Chem.*, 1981, **53**, 2401. However, our results are similar to those obtained by these authors under dilute tributylstannane conditions.
12. D.P. Curran, R.L. Wolin, *Synlett*, 1991, 317; see also G.A. Molander, J.B. Etter, *J. Am. Chem. Soc.*, 1987, **109**, 6556; T. Imamoto, Y. Kamiya, T. Hatajima, H. Takahashi, *Tetrahedron Lett.*, 1989, **30**, 5149.
13. Small amounts of hydrolysed ketone were also observed in these trapping experiments.

(Received in UK 22 August 1991)