

Tetrahedron Letters 42 (2001) 2047-2049

TETRAHEDRON LETTERS

Alkoxy radical accelerated β-fragmentation of alcohols and lactols

James H. Rigby,* Anne Payen and Namal Warshakoon

Department of Chemistry, Wayne State University, Detroit, MI 48202, USA Received 6 December 2000; accepted 17 January 2001

Abstract—Treatment of alcohols and lactols with $Pb(OAc)_4/Cu(OAc)_2$ in refluxing benzene provides the corresponding δ -unsaturated carbonyl products. © 2001 Elsevier Science Ltd. All rights reserved.

Radical-mediated fragmentation of hydroxyl group based functionalities has been an area of considerable activity over the years.¹ In conjunction with a recent synthesis of (+)-estradiol, we required a fragmentation method that would involve direct production of an alkene during the bond-breaking step.² After considerable experimentation, it was discovered that a combination of Pb(OAc)₄ with a catalytic quantity of Cu(OAc)₂ efficiently converted compound **1** into **2**,³ which was subsequently transformed into the steroid via a novel higher-order cycloaddition–Ramberg–Bäcklund sequence (Eq. (1)). Related conditions had been briefly examined previously for the cleavage of alcohols,⁴ and Pb(OAc)₄ is, of course, well known to effect decarboxylation of carboxylic acids.⁵ An extensive examination of the scope and limitations of this fragmentation process has been conducted and the results of this study are detailed below.⁶ While, in general, simple alcohol substrates were found not to be viable fragmentation participants, a range of strained alcohols and lactols proved to be effective reactants.

In a typical example, cleavage of lactol 3^7 under the mixed Pb(IV)/Cu(II) conditions afforded the corresponding bicyclic alkene–formate 4^3 in serviceable yields (Eq. (2)). In many cases mixtures of fragmentation products were produced. For instance, (–)-borneol provided a mixture of isomeric fragmentation products **6** and 7 in good yield⁸ (Eq. (3)), and the closely related substrate, fenchyl alcohol, gave a mixture of ring cleaved



Keywords: fragmentation reactions; radicals and radical reactions; alcohols; alkenes. * Corresponding author.

0040-4039/01/\$ - see front matter @ 2001 Elsevier Science Ltd. All rights reserved. PII: S0040-4039(01)00121-6



14

products comprised of all possible double bond isomers in 50% yield.

In another illustration of the general nature of these conditions, the fragmentation of bicyclic lactols $8a^9$ and $8b^{10}$ gave the expected ring-cleaved lactones 9a and $9b^3$ in good yield without incident (Eq. (4)).

Interestingly, the corresponding phenyl substituted lactol $8c^{11}$ afforded the expected fragmentation product $9c^{3}$ accompanied by a moderate amount of the spirolactone 10^{3} (Eq. (5)). The latter compound is presumably derived from a competitive homolytic aromatic substitution process,¹² or, alternatively, it may be formed by trapping of a carbocation intermediate produced during the bond breaking event. Efforts to increase the proportion of 10 relative to 9c by adjusting the ratio of Pb(OAc)₄:Cu(OAc)₂ were not successful.

Yet another intriguing side-reaction was observed during attempted fragmentation of the bicyclic lactols **11a** and **11b**. Each material led, on exposure to the standard fragmentation conditions, to a moderate amount of the desired lactone along with varying quantities of an interesting spirocyclic ether by-product. Thus, lactol **11a** yielded cleavage product **12a** as well as a small quantity of ether **13a**¹³ (Eq. (6)), while **11b** gave a much higher overall yield of products (Eq. (7)), now favoring the production of ether **13b**³ over the corresponding lactone, **12b**.³

In contrast, compound 14, which appears to exist exclusively in the opened keto-alcohol form, gave only the corresponding spiro-ether $13c^3$ in 34% yield (Eq. (8)). This observation provides support for the notion that

the ring-opened forms of **11a** and **11b** lead to **13a** and **13b**, respectively, via a hydrogen atom extraction–electron transfer–trapping sequence.¹⁴

34%

(8)

13c

ΩН

In conclusion, a new and versatile method for alcohol and lactol fragmentation has been developed using a mixture of $Pb(OAc)_4/Cu(OAc)_2$ in refluxing benzene.

Acknowledgements

The authors wish to thank the National Institutes of Health (GM-30771) for their generous support of this research.

References

For some leading references to other fragmentation procedures, see: (a) HgO/I₂: Suginome, H.; Yamada, S. J. Org. Chem. 1985, 50, 2489; Tetrahedron 1987, 43, 3371; (b) Pb(OAc)₄/I₂: Fuhrer, H.; Lorenc, L.; Pavlovic, V.; Rihs, G.; Rist, G.; Kalvoda, J.; Mihailovic, M. Lj. Helv. Chim. Acta 1981, 64, 703; (c) IBDA/I₂: Freire, R.; Marrero, J. J.; Rodríguez, M. S.; Suárez, E. Tetrahedron Lett. 1986, 27, 383; (d) Iodosyl-benzene/I₂: Arrmas, P.; Francisco, C. G.; Suárez, E. Tetrahedron Lett. 1993, 34, 7331; (e) FeSO₄/Cu(OAc)₂: Schreiber, S. L. J. Am. Chem. Soc. 1980, 102, 6163; (f) Pb(OAc)₄ with γ-hydroxyalkylstannanes: Nakatani, K.; Isoe, S. Tetrahedron Lett. 1984, 25,

5335; (g) Mn(OAc)₃/Cu(OAc)₂: Heiba, E. I.; Dessau, R. M. J. Am. Chem. Soc. **1971**, *93*, 524.

- Rigby, J. H.; Warshakoon, N. C.; Payen, A. J. J. Am. Chem. Soc. 1999, 121, 8237.
- All new compounds exhibited spectral (¹H NMR, ¹³C NMR, IR) and analytical (combustion analysis and/or HRMS) data fully consistent with the assigned structures.
- (a) Kapustina, N. I.; Popkov, A. Y.; Gasanov, R. G.; Nikishin, G. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1988, 2327; (b) Kapustina, N. I.; Soejtirm, S. S.; Nikishin, G. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1984, 2721; (c) Nikishin, G. I.; Kapustina, N. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1984, 1345.
- 5. Sheldon, R. A.; Kochi, J. K. Org. React. 1972, 19, 279.
- 6. Typical experimental procedure: An oven dried flask equipped with a water reflux condenser was charged with a lactol (1 equiv.), lead tetraacetate (1.6 equiv.), copper(II) acetate (0.18 equiv.), pyridine (1.2 equiv.) and benzene. The

mixture was heated to reflux while monitoring the progress of the reaction by TLC (mixture turns blue-green when the reaction is completed, ca. 20 min). At completion of the reaction, the mixture was filtered through a thin pad of Celite.

- 7. Suginome, H.; Yamada, S. Synthesis 1986, 741.
- For a related result with Pb(OAc)₄ in the absence of Cu(OAc)₂, see: Partch, R. E. J. Org. Chem. 1963, 28, 276.
- Sassaman, M. B.; Prakash, G. K. S.; Olah, G. A. Tetrahedron 1988, 44, 3771.
- Kobayashi, K.; Sasaki, A.; Kanno, Y.; Suginome, H. *Tetrahedron* 1991, 47, 7245.
- 11. Lyttle, M. H.; Streitwieser, A.; Miller, M. J. J. Org. Chem. 1989, 54, 2331.
- 12. Harvey, D. R.; Norman, R. O. C. J. Chem. Soc. 1964, 4860.
- Paquette, L. A.; Negri, J. T.; Rogers, R. D. J. Org. Chem. 1992, 57, 3947.
- 14. Mihailovic, M. Lj.; Cekovic, Z. Synthesis 1970, 209.