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Radical Oxidative Decarboxylation of α-Hydroxylactones. Influence of Oxygen-Carbon β-Bond Effect

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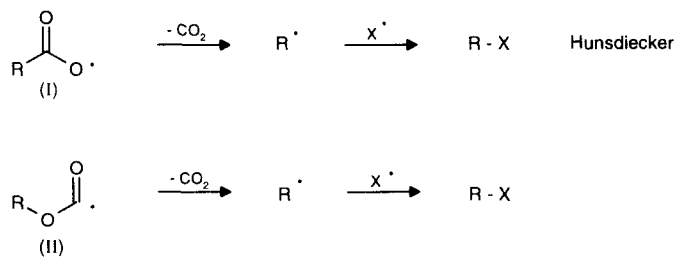
Abstract: α-Hydroxylactones undergo decarboxylation when submitted to the system (diacetoxyiodo)benzene (DIB)/iodine under mild conditions. β-Oxygen substituents were observed to deactivate the decarboxylation reaction.

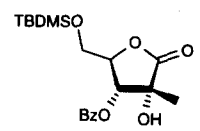
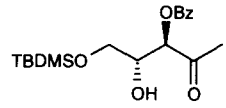
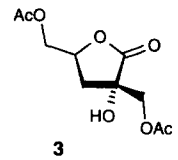
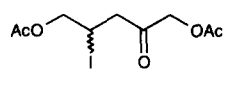
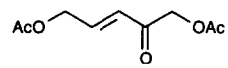
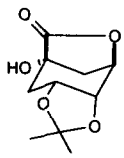
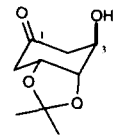
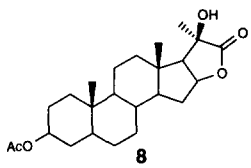
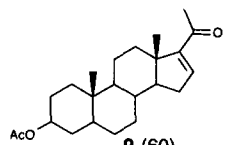
The decarboxylation of organic acids, usually under oxidative or reductive conditions, with concomitant replacement by a halogen, through a radical intermediate, in the Hunsdiecker[1] or modified Hunsdiecker reaction,[2] comprises a useful and selective procedure for the synthesis of halogenated substances.

Scheme 1



We have reported previously[3] the use of a hypervalent iodine reagent, (diacetoxyiodo)benzene, in order to promote the iododecarboxylation of carboxylic acids to alkyl iodides. This procedure, as are other radical methods,[4] is based on the formation of a carboxyl radical (I) in the free acid that evolves CO_2, as shown in Scheme 1 to give an alkyl radical that can subsequently be trapped by a halogen radical. On the other hand, to the best of our knowledge, the formation of alkoxycarbonyl radicals (II) has not been reported under oxidative conditions. We conceived the possibility of decarboxylating a lactonised acid by breaking the C-CO bond, provided that we could create an α-alkoxy radical able to promote a β-fragmentation reaction. It is known that alkoxycarbonyl radicals derived from tertiary alcohols are fragmented quite readily to give deoxygenated products in good yields;[5] however, the literature suggests that such radicals from secondary alcohols are thermally stable, unless the derived carbon radicals are specially stabilised.[6a] In fact, high temperatures (130-180 °C) and, usually, low yields of decarboxylated products were observed in the examples reported.[6b] Indeed, Togo *et al.*[7] report that primary and secondary alkoxycarbonyl radicals, instead of undergoing decarboxylation are stable enough to trap intramolecularly an olefinic double bond to give lac-

Table. β-Fragmentation of α-Hydroxylactones by DIB.[19]

Entry	Substrate	Solvent	Reagents (mmol)[a]	Conditions		Products (Yield %)
				Time (h)	Temp. (°C)	
1	 **1**	Cy	1.2/1.2	4	40	 **2** (75)
2[b]	 **3**	CH_2Cl_2	1.2/1	2	r.t.	 **4** (25)  **5** (51)
3	 **6**	CCl_4	1.2/1	1.5	55	 **7** (64)
4	 **8**	Cy	1.6/1	2	58	 **9** (60)

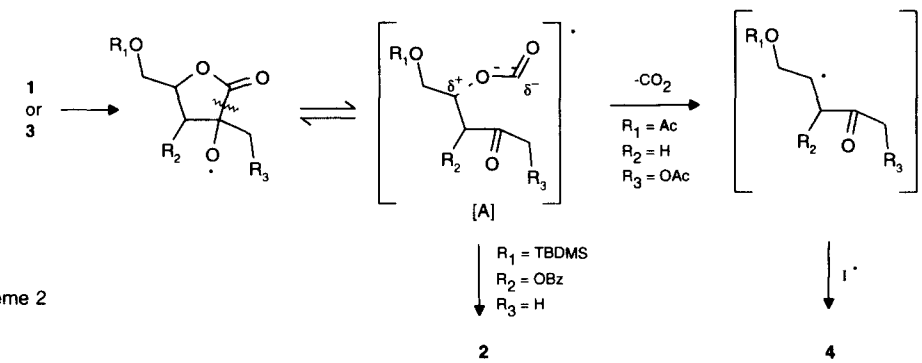
[a] Mmoles of (diacetoxyiodo)benzene/mmoles of iodine per mmol of substrate. [b] In this experiment some starting material was recovered (20%). TBDMS = *tert*-butyldimethylsilyl, Cy = cyclohexane.

one derivatives. Since we have shown that DIB/I_2 is a good system for obtaining alkoxy radicals,[8] we decided to submit several α-hydroxy-γ- and δ-lactones to this reagent in order to form secondary alkoxycarbonyl radicals. The incidence of the oxygen-carbon β-bond effect in radical reactions is well known and has been widely discussed.[9] It has been suggested that β-bonded oxygen influences the stability of the intermediate carbon-centred radical favouring its formation as in the Barton-McCombie deoxygenation,[9b] or opposing it, as occurs in the hydrogen atom abstraction from ethers by *tert*-butoxyl radicals.[9c] This apparent contradiction is explained in terms of different polar effects in the proposed intermediates. We chose the substrates also with the aim of observing the inductive effect of the β-oxygen substituents on the decarboxylation reaction.

The glucosaccarinic lactone derivative **1**[10] when treated with DIB/I_2 at 40 °C undergoes C_1-C_2 cleavage to give the 1-deoxyribulose derivative **2**[11] in good yield, being detected as only one isomer by NMR, this chiral product with 1,2-diol substructure can be an interesting building block. When the reaction was performed with isosaccarinic lactone diacetate **3**[12] this took place at room temperature to give a mixture of the iododerivative **4**[13] and the predominant α,β-unsaturated ketone **5**.[14] With the quinic acid δ-lactone de-

rivative **6**[15] the reaction with DIB/I_2 leads to the alcohol **7**,[16] with retention of configuration in C-3 as indicated by the NMR signal at 4.24 ppm, where the coupling constant $J_{3,4}$ 2.8 Hz, obtained by decoupling experiments, shows the equatorial configuration of H-3. A derivative of this polyalcohol has been used previously as a chiral intermediate in the synthesis of some antibiotics.[17] When the substrate used was the steroid γ-lactone **8**[18a] the sole product observed was the α,β-unsaturated ketone **9**.[18b]

If we compare the reaction of substrate **3** with that of **1** which shows an additional β-oxygen effect in carbon-3 (entries 1 and 2), we deduce that this effect does not favour the decarboxylation. This is corroborated by the reactions of quinic acid lactone **6** (entry 3) that does not undergo decarboxylation, with β-oxygen effect, and also by the substrate **8** (entry 4) that, lacking that inductive effect, is decarboxylated. A plausible explanation of this behaviour can be reached if we accept a dipolar transition state [A], similar to that proposed for the Barton-McCombie deoxygenation,[9b] as shown in Scheme 2, where the carbon atom exhibits a fractional positive charge, which would be destabilised by the inductive effect of the β-oxygen substituent.



Scheme 2

In the Scheme 2 is shown a possible mechanism to explain this reaction. The alkoxy radical initially formed undergoes β-fragmentation to give the intermediate [A] that, when R_2 is an oxygenated function, is able to trap a radical originated in the reaction to form an ester that would then be hydrolysed to the alcohol derivative (*e.g.* **2** and **7**). When R_2 = H the intermediate [A] is decarboxylated and the radical is also stabilised by an iodine radical from the medium that could be isolated (like **4**) or eliminated ultimately to the olefinic products (*e.g.* **5** and **9**).

In summary this unprecedented reaction of decarboxylation of α-hydroxylactones is mechanistically interesting, because it is based on a C-C cleavage originated by a radical located outside of the carboxyl group, is performed under non-photochemical mild conditions[19] and does not depend on the ring size (γ- or δ-lactone) in the studied cases, being compatible with several protective groups.

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REFERENCES AND NOTES

1. Johnson, R. G.; Ingham, R. K. *Chem. Rev.* **1956**, *56*, 219. Wilson, C. V. *Org. React.* (N.Y.) **1959**, *9*, 332.
2. Sheldon, R. A.; Kochi, J. K. *Org. React. (N.Y.)* **1972**, *19*, 279. Barton, D. H. R.; Faro, H. P.; Serebryakov, E. P.; Woolsey, N. F. *J. Chem. Soc.* **1965**, 2438. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds;* Pergamon Press: Oxford, 1986. Minisci, F.; Vismara E.; Fontana F. *Heterocycles* **1989**, *28*, 489. Fontana F.; Minisci, F.; Barbosa, M. C. N.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866. Minisci, F.; Vismara, E.; Fontana, F. *J. Heterocycl. Chem.* **1990**, *27*, 79. Barton, D.

H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901. Barton, D. H. R. *Aldrichimica Acta* **1990**, *23*, 3. Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413 and references cited therein.

3. Concepción, J. I.; Francisco, C. G.; Freire, R.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1986**, *51*, 402.
4. Crich, D. In *Comprehensive Organic Synthesis, Vol. 7*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; p 717 and references cited therein.
5. Crich, D.; Fortt, S. *Synthesis*, **1987**, 35. An efficient decarboxylation of some chloroformate derivatives from primary and secondary alcohols, under reductive conditions, has been reported: Jackson R.; Malek, F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1207.
6. a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1975. b) Barton, D. H. R.; Crich, D. *J. Chem. Soc., Chem. Commun.* **1984**, 774.
7. Togo, H. and Yokoyama, M. *Heterocycles* **1990**, *31*, 437.
8. Francisco, C. G.; Freire, R.; Rodríguez, M. S.; Suárez E. *Tetrahedron Lett.* **1987**, *28*, 3397. Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772. Armas, P.; Francisco, C. G.; Suárez, E. *J. Amer. Chem. Soc.* **1993**, *115*, 8865. Boto, A.; Betancor, C.; Prangé, T.; Suárez, E. *J. Org. Chem.* **1994**, *59*, 4393.
9. a) Barton, D. H. R.; Hartwig, W.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1982**, 447. Dupois, J.; Giese B.; Ruegge, D.; Fischer, H.; Korth, H. G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896. Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, *22*, 144. b) Jenkins, I. D. *J. Chem. Soc., Chem. Commun.* **1994**, 1227. c) Busfield, W. K.; Grice, I. D.; Jenkins, I. D.; Monteiro, M. J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1071. Busfield, W.K.; Grice, I. D.; Jenkins, I. D. *ibid.* **1994**, 1079.
10. Glucosaccarinic lactone prepared as described by Whistler, R. L.; BeMiller, J. N. In *Methods in Carbohydrate Chemistry, Vol. II*; Whistler, R. L.; Wolfrom, M. L., Eds.; Academic Press: San Diego, 1963; p 484. Lactone was treated with t-BuDMSCl and imidazol, and then benzoylated with benzoyl chloride to give substrate (**1**): m.p. 82-84 °C, $[\alpha]_D$ 41.6°.
11. Compound (**2**): $[\alpha]_D$ -17° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3560, 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 8.05 and 7.50 (5H, m, Ar), 5.21 (1H, d, *J* 6 Hz, H-3), 4.15 (1H, ap q, *J* 5.5 Hz, H-4), 3.84 (1H, dd, *J* 4.5, 10.5 Hz, H_a-5), 3.78 (1H, dd, *J* 5.4, 10.5 Hz, H_b-5), 2.32 (3H, s, H-1), 0.88 (9H, s, t-$BuMe_2Si$), 0.68 and 0.52 (6H, s, t-$BuMe_2Si$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 204.9 (s), 166.0 (s), 133.6 (d), 129.8 (d), 128.5 (d), 78.1 (d), 71.6 (d), 63.2 (t), 28.6 (d), 25.8 (q), -5.48 (q), -5.52 (q). EIMS (m/z), 353 (M^+-1, 21), 335 (67), 295 (56).
12. Prepared as described by Whistler R. L.; BeMiller, J. N. In *Methods in Carbohydrate Chemistry*; *Vol. II*; Whistler, R.L.; Wolfrom, M. L., Eds.; Academic Press: San Diego, 1963; p 477.
13. Compound (**4**): $[\alpha]_D$ -5° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 4.69 (2H, s, H-1), 4.33 (1H, m, H-4), 4.06 (1H, dd, *J* 5.8, 11.5 Hz, H_a-5), 4.14 (1H, dd, *J* 3.7, 11.5 Hz, H_b-5), 2.69 (1H, dd, *J* 7.7, 16.9 Hz, H_a-3), 2.58 (1H, dd, *J* 4.5, 16.9 Hz, H_b-3), 2.18 (3H, s, -OAc), 2.11 (3H, s, -OAc); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 203.1 (s), 171.0 (s), 170.3 (s), 68.3 (t), 67.2 (t), 65.8 (d), 42.1 (t), 20.8 (q), 20.4 (q). EIMS (m/z), 201 (M^+-I, 68), 159 (54), 145 (55), 141 (100).
14. Compound (**5**): IR ($CHCl_3$) ν_{max} 1750, 1700, 1645 cm^{-1}; UV (EtOH) λ_{max} 217 nm (ε 5770); ^1H NMR (200 MHz, $CDCl_3$) δ_H 6.92 (1H, ddd, *J* 16, 4.5, 4.5 Hz, H-4), 6.35 (1H, brd, *J* 16 Hz, H-3), 4.84 (2H, s, H-1), 4.77 (2H, aq, *J* 4.5 Hz, H-5), 2.19 (3H, s, OAc), 2.14 (3H, s, OAc); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 191.7 (s), 170.2 (s), 140.7 (d), 125.4 (d), 67.1 (t), 62.6 (t), 20.7 (q), 20.5 (q); EIMS (m/z) 201 (M^++1, 20), 179 (15), 173 (10), 167 (17), 141 (94).
15. Lesnuisse, D; Berchtold, G. A. *J. Org. Chem.* **1985**, *50*, 888.
16. Compound (**7**): $[\alpha]_D$ 127° ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3610, 1715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 4.71 (1H, m, H-4), 4.24 (1H, m, H-3), 2.79 (1H, dd, *J* 17.3, 2.7 Hz, H_a-6), 2.62 (1H, dd, *J* 17.3, 3.6 Hz, H_b-6), 2.63 (1H, dd, *J* 17.6, 2.7 Hz, H-2), 2.42 (1H, ddd, *J* 17.6, 3.6, 1.7 Hz, H-2), 1.36 and 1.44 (3H each, s, isoprop.). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 207.7 (s), 108.7 (s), 75.0 (d), 72.2 (d), 68.2 (d), 41.5 (t), 40.1 (t), 26.3 (q), 23.8(q); EIMS (m/z): 187 (M^++1, 22), 171 (100).
17. Cleophax, J.; Gero, S. D.; Leboul, J.; Akhtar, M.; Barnett, J. E. G.; Pearce, C. J. *J. Amer. Chem. Soc.* **1976**, *98*, 7110.
18. a) González, A. G.; Freire, R.; Francisco, C. G.; Salazar, J. A.; Suárez, E. *Tetrahedron* **1973**, *29*, 1731. b) *Dictionary of Steroids*; Hill, R. A.; Kirk, D. N.; Makin, H. L. J.; Murphy, G. M., Eds.; Chapman and Hall: London, 1991; p. 615.
19. In a typical experiment, isosaccarinic lactone diacetate **3** (20 mg, 0.08 mmol) was solved in dichloromethane (3 ml), and (diacetoxyiodo)benzene (32 mg, 0.1 mmol) and iodine (10.5 mg, 0.08 mmol) were added and the resulting suspension was stirred, under argon, at room temperature for 2.5 h. Then, the reaction crude was passed directly trough a silica gel column chromatography (*n*-hexane, *n*-hexane/ethyl acetate, 70/30) and the iododerivative **4** (6.6 mg) and the unsaturated ketone **5** (8.3 mg), with minor amounts (4 mg) of starting material, were isolated.

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