A Mild and Efficient Oxidation of Primary Alkyl Iodides to Carboxylic Acids

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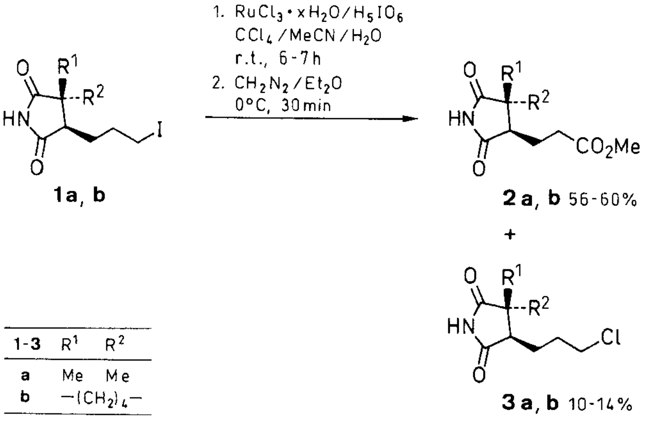
Received 24 October 1991

A one-step method for the preparation of carboxylic acids from primary alkyl iodides by treatment with ruthenium tetroxide is described.

Non-activated organic iodides are inert to a number of oxidizing agents but are converted into the corresponding alcohols by treatment with 3-chloroperoxybenzoic acid.[1] A number of methods are known for the oxidation of primary hydroxy compounds into carboxylic acids.[2] To the best of our knowledge the conversion of primary alkyl iodides into carboxylic acids is unprecedented and up to now this transformation required a several-step sequence. In the course of our studies[3] directed towards the synthesis of methyl 3-(methoxycarbonylmethyl)-3-methyl-2-succinimidepropanoate,[4] the key building block required for the synthesis of isobacteriochlorin pigments,[4,5] we required a mild procedure for the preparation of carboxylic acids from primary alkyl iodides on 2,3-substituted succinimides, that on the other hand can be obtained by a recently described method.[6] Several oxidant reagents were studied in an attempt to perform this reaction and ruthenium tetroxide, a widely recognized organic oxidant,[7] was found to be useful to conduce this transformation. The succinimides **1a,b** gave, after methylation, the acid derivatives **2a,b**, in good yield (Scheme 1),[8] together with small amounts of the chloro derivatives **3a,b** (10 and 14%, respectively). The steroidal alkyl iodide **4** was also transformed into the carboxylic acid **5** in good yield (Scheme 2), while the homologous primary alkyl bromide **6** proved to be inert, after 24 hours, to the action of this reagent.



1a, b

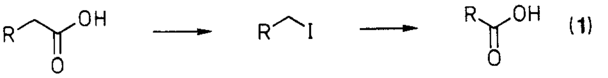
2a, b 56-60%

3a, b 10-14%

1-3	R^1	R^2
a	Me	Me
b	$-(CH_2)_4-$	

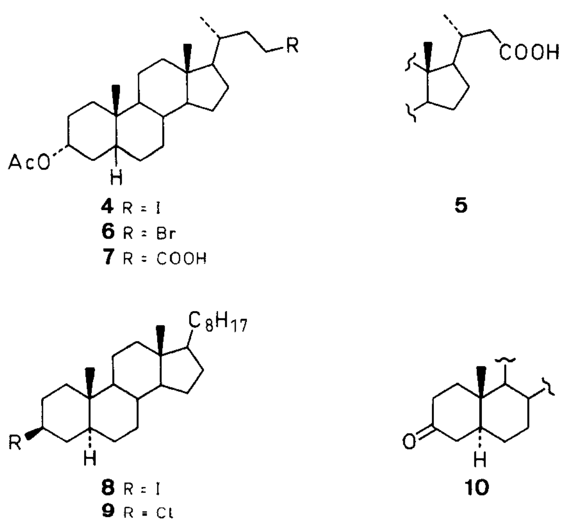
Scheme 1

The sequence iododecarboxylation of primary carboxylic acids[9] followed by ruthenium tetroxide oxidation of the alkyl iodides so obtained can be useful in organic synthesis for transforming carboxylic acids into the corresponding acids with one fewer carbon atom (eq. 1). Thus, compound **5** was obtained from the parent **7** in 66% overall yield, by these two steps.



(1)

Although the present method works well with primary alkyl iodides it is less suitable for secondary ones. Thus,



4 R = I
6 R = Br
7 R = COOH

5

8 R = I
9 R = Cl

10

Scheme 2

Table. Oxidation of Alkyl Iodides with Ruthenium Tetroxide

Substrate	Products	Time (h)	Yield[a] (%)	mp (°C) (solvent)	IR ($CHCl_3$) ν (cm^{-1})	MS (70 eV) m/z (%)	Molecular Formula[b] or Lit. mp (°C)	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ[c]
1a	**2a**	6	56	67–68.5 (EtOAc/hexane)	3402, 1781, 1725	213 (M^+, 8), 198 (16), 181 (78), 166 (86), 82 (100)	$C_{10}H_{15}NO_4$ (213.2)	1.23 (s, 3H, 3-CH_3), 1.34 (s, 3H, 3-CH_3), 1.94 (m, 3H, 2-H, 2'-H_2), 2.70 (m, 2H, 1'-H_2), 3.70 (s, 3H, OCH_3), 8.14 (m, 1H, NH)	20.94 (t), 21.03 (q), 24.19 (q), 31.79 (t), 44.61 (s), 50.47 (d), 51.63 (q), 173.26 (s), 179.06 (s), 183.24 (s)
	3a		10	76–78 (acetone/pentane)	3402, 1781, 1724	206/204 (M^++1, 3 : 9), 168 (62), 97 (73), 69 (100)	$C_9H_{15}ClNO_2$ (204.7)	1.23 (s, 3H, 3-CH_3), 1.35 (s, 3H, 3-CH_3), 1.84 (m, 3H), 2.19 (m, 1H), 2.51 (t, 1H, J = 7.2, 2-H), 3.60 (m, 2H, 3'-H_2), 8.44 (m, 1H, N–H)	21.11 (q), 23.37 (t), 24.70 (q), 30.77 (t), 44.62 (t), 44.94 (s), 51.18 (d), 178.50 (s), 182.80 (s)
1b	**2b**	7	60	oil	3402, 1776, 1727	329 (M^+, 12), 207 (83), 198 (28), 179 (39), 166 (100)	$C_{12}H_{17}NO_4$ (239.3)	1.85 (m, 9H), 2.17 (m, 1H), 2.66 (m, 3H), 3.68 (s, 3H, OCH_3), 8.48 (m, 1H, N–H)	22.57 (t), 25.34 (t), 25.65 (t), 31.28 (t), 31.47 (t), 38.28 (t), 49.88 (d), 51.68 (q), 55.02 (s), 173.28 (s), 179.01 (s), 183.14 (s)
	3b		14	68–70 (acetone/pentane)	3401, 1775, 1722	232/230 (M^++1, 1 : 3), 194 (83), 190/188 (28 : 83), 81 (83), 67 (100)	$C_{11}H_{17}ClNO_2$ (230.7)	1.82 (m, 10H), 2.12 (m, 2H), 2.59 (t, 1H, J = 6.9, 2-H), 3.60 (m, 2H, 2'-H_2), 7.70 (m, 1H, N–H)	24.89 (t), 25.33 (t), 25.66 (t), 30.12 (t), 31.08 (t), 38.72 (t), 44.59 (t), 50.34 (d), 55.02 (s), 179.20 (s), 183.21 (s)
4	**5**	24	68	170–174 ($CHCl_3$/MeOH)	3512, 3461–2393, 1708	404 (M^+, 1), 386 (1), 344 (100), 215 (97)	$C_{25}H_{40}O_4$ (404.6)	0.69 (s, 3H, 13-CH_3), 0.93 (s, 3H, 10-CH_3), 1.00 (d, 3H, J = 6.3, 20-CH_3), 2.03 (s, 3H, $OCOCH_3$), 4.72 (m, 1H, 3β-H)	12.02 (q), 19.47 (q), 20.77 (t), 21.43 (q), 23.28 (q), 24.12 (t), 26.27 (t), 26.59 (t), 26.96 (t), 28.27 (t), 32.21 (t), 33.58 (d), 34.54 (s), 34.99 (t), 35.75 (d), 39.99 (t), 40.35 (d), 41.31 (t), 41.83 (d), 42.78 (s), 55.98 (d), 56.48 (d), 74.39 (d), 170.72 (s), 179.52 (s)
8	**9**	6	12	113–114 (acetone)			112[10]		
	10		36	130–132 (EtOH)			128–129[11]		

[a] Yield of products isolated after chromatography.

[b] Satisfactory HRMS obtained: m/z ±0.0021.

[c] Multiplicities were determined by DEPT experiments.

when the reaction was performed with 3β-iodo cholestane (**8**), 3β-chlorocholestane (**9**)[10] and cholestan-3-one (**10**)[11] were obtained in moderate yield (12 and 36%, respectively) (Scheme 2).

As in the case of the oxidation of alkyl iodides with 3-chloroperoxybenzoic acid,[1] an iodoso derivative can be an intermediate which rearranges to a hypoiodite which is converted into the alcohol compound under reaction conditions and this is subsequently oxidized by the excess of ruthenium tetroxide.

In conclusion, we have developed a simple, convenient and general one-step procedure to prepare carboxylic acids from primary alkyl iodides.

The starting materials were prepared according to the following procedures: (3-iodopropyl)succinimide (**1a**) as described previously[6] while **1b** was obtained analogously;[12] 23-iodo- and 23-bromo-24-nor-5β-cholan-3α-yl acetates (**4**)[9] and (**6**)[13] from 3β-acetoxycholan-24-oic acid (**7**) (Sigma Chemical Co.); 3β-iodocholestane (**8**) by standard procedure from (+)-dihydrocholesterol (Aldrich Chemical Co.) by treatment with p-TsCl and NaI of the intermediate tosyl derivative. Commercial solvents were of analytical grade and were used without further purification. $RuCl_3 \cdot H_2O$ and periodic acid were purchased from Janssen Chimica and Ega Chimie, respectively. TLC analyses were conducted on silica gel plates (Schleicher and Schüll F 1500/LS 254) and were visualized by spraying with Dragendorff's reagent (Sigma Chemical Co.) or with 0.5% vanillin in H_2SO_4/EtOH (4:1) and further heating until development of color. Silica gel 0.063–0.2 mm for column chromatography and 60 PF 254 for quick chromatography on a Harrison

Chromatotron were purchased from Merck. Melting points were taken using a Kofler hot-stage apparatus and are uncorrected and observed rotations at the Na-D line were obtained using a Perkin-Elmer 241 polarimeter. Low resolution mass spectra were obtained using Hewlett Packard 5930 A and Micromass ZAB-2F spectrometers and high resolution mass spectra on a VG Micromass ZAB-2F spectrometer. IR spectra were obtained using a Perkin-Elmer IR 1600/FTIR spectrophotometer. ^{1}H NMR spectra were obtained using Bruker AC 80 (80 MHz) and Bruker WP 200 SY (200 MHz) spectrometers. ^{13}C NMR spectra were obtained using Bruker AC 80 (20.1 MHz) and Bruker WP 200 SY (50.3 MHz) spectrometers.

Reaction of Alkyl Iodides with Ruthenium Tetroxide; General Procedure:

A round-bottomed flask equipped with a Teflon-covered magnetic stirring bar, was charged with RI (0.1 mmol), CCl_4 (0.3 mL), MeCN (0.3 mL), H_2O (0.45 mL) and H_5IO_6 (94 mg, 0.41 mmol, 4.1 equiv). (Solvent was 2.6, 2.6, 3.9 mL for steroidal alkyl halides **4** and **6**, and 0.6, 0.6, 0.9 mL for **8**). The flask content was stirred for 15 min, $RuCl_3 \cdot xH_2O$ (0.8 mg, 0.04 equiv) was added, the mixture was stirred at r.t. for 6–24 h, and cooled to 0 °C with an ice bath. Et_2O (2 mL) was then added while vigorous stirring was continued for 10 min. The flask content was extracted with Et_2O (3 × 5 mL) and the organic phase washed with brine (4 × 5 mL) and dried (Na_2SO_4). The solvent was evaportaed and the crude product purified by chromatography. In the case of succinimides **1a,b** the crude residue dissolved in Et_2O (5 mL) was treated with excess ethereal CH_2N_2 and then purified. In all cases eluants: hexane/EtOAc (results in Table).

This work was supported by the Investigation Programme N° PB0406 of the Dirección General de Investigación Científica y Técnica.

(1) Reich, H.J.; Peake, S.L. *J. Am. Chem. Soc.* **1978**, *100*, 4888.
Macdonald, T.L.; Narashimhan, N.; Burka, L.T. *J. Am. Chem. Soc.* **1980**, *102*, 7760.

(2) Larock, R.C. In *Comprehensive Organic Transformations: a Guide to Functional Group Preparations*; VCH Publishers, Inc.: New York, 1989; p 843.

(3) Hernández, R.; Melián, D.; Suárez, E., unpublished results.

(4) Whittingham, W.G.; Ellis, M.K.; Guerry, P.; Henderson, G.B.; Müller, B.; Taylor, D.A.; Leeper, F.J.; Battersby, A.R. *J. Chem. Soc., Chem. Commun.* **1989**, 1116.
Müller, B.; Collins, A.N.; Ellis, M.K.; Whittingham, W.G.; Leeper, F.J.; Battersby, A.R. *J. Chem. Soc., Chem. Commun.* **1989**, 1119.
Battersby, A.R.; Westwood, S.W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1679.

(5) Turner, S.P.D.; Block, M.H.; Sheng, Z-C.; Zimmerman, S.C.; Battersby, A.R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1577.
Block, M.H.; Zimmerman, S.C.; Henderson, G.B.; Turner, S.P.D.; Westwood, S.W.; Leeper, F.J.; Battersby, A.R. *J. Chem. Soc., Chem. Commun.* **1985**, 1061.

(6) Hernández, R.; Marrero, J.J.; Melián, D.; Suárez, E. *Tetrahedron Lett.* **1988**, *29*, 6661.

(7) Lee, D.G.; van der Engh, M. In *Oxidation in Organic Chemistry*; Trahanovsky, W.S. Ed.; Academic Press: New York, 1973; Part B, Chapter 4.
Gore, E.S. *Platinum Met. Rev.* **1983**, *27*, 111.

(8) Compounds **1–3** are racemates, but in Scheme 1 one of the enantiomers is shown.

(9) Concepción, J.I.; Francisco, C.G.; Freire, R.; Hernández, R.; Salazar, J.A.; Suárez, E. *J. Org. Chem.* **1986**, *51*, 402.

(10) Marker, R.E.; Whitmore, F.C.; Kamm, O. *J. Am. Chem. Soc.* **1935**, *57*, 2358.

(11) Beereboom, J.J.; Djerassi, C.; Ginsburg, D.; Fieser, L.F. *J. Am. Chem. Soc.* **1953**, *75*, 3500.

(12) Hernández, R.; Melián, D.; Suárez,E., unpublished results.

(13) Wiberg, K.B.; Matturro, M.G.; Okarma, P.J.; Jason, M.E. *J. Am. Chem. Soc.* **1984**, *106*, 2194.