Pergamon

Tetrahedron 54 (1998) 6751–6756

TETRAHEDRON

A Practical Decarboxylative Hydroxylation of Carboxylic Acids

Derek H. R. Barton,[a*] Stéphane D. Géro,[b] Pascale Holliday,[b] Béatrice Quiclet-Sire,[b] and Samir Z. Zard[b,c]

a) Department of Chemistry, Texas A&M University, College Station, Texas 77843, U. S. A.

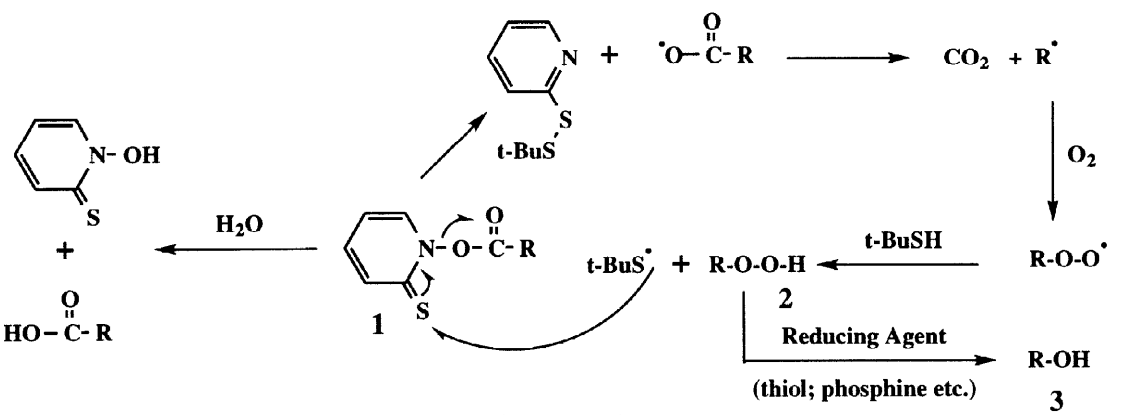
b) Institut de Chimie des Substances Naturelles, C. N. R. S., 91198 Gif-Sur-Yette, France

c) Laboratoire de Synthèse Organique associé au CNRS Ecole Polytechnique, 91128 Palaiseau, France

Received 9 February 1998; accepted 10 April 1998

Abstract : Irradiation of esters of N-hydroxy-2-thiazolinethione under air or oxygen at room temperature in the presence of tert-dodecanethiol affords the corresponding nor-alcohols after a reductive work-up.

Carboxylic acids are ubiquitous in nature. New reactions that allow the manipulation of the carboxylic acid function open up therefore vast possibilities for the modification and synthesis of natural products. One important transformation is the conversion of a carboxylic group into an alcohol with one less carbon atom. Such a decarboxylative hydroxylation has hitherto proven difficult to accomplish by classical ionic methods[1] or, until recently, even by a radical based process. The decomposition of acyl peroxides in the presence of oxygen[2a,b] or their Baeyer-Villiger type rearrangement[2c] were essentially the only direct methods for performing this transformation. However, the discovery of the Barton decarboxylation reaction using thiohydroxamate esters provided a simple and general solution to this long-standing synthetic problem.[3]



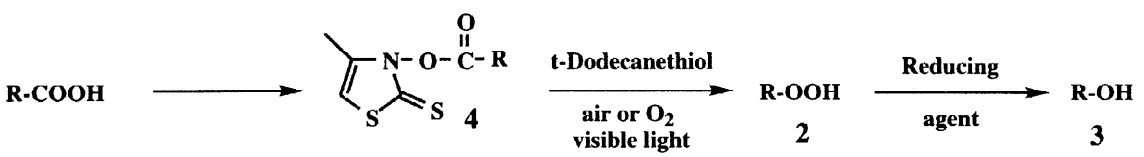
Scheme 1

In a first modification,[4] the N-hydroxythiopyridone ester **1**, either pre-formed or generated *in situ* (by addition of an acid chloride to a suspension of the sodium salt of N-hydroxythiopyridone) is photolysed by irradiation with a tungsten lamp in the presence of *tert*-butyl mercaptan with a strong stream of oxygen

0040-4020/98/$19.00
PII: S0040-4020(98)00337-8

bubbling through the medium. As shown in scheme 1, the carbon radical produced upon decarboxylation is captured with triplet oxygen, and the ensuing hydroperoxy radical is quenched by the thiol to give finally a hydroperoxide **2** which may be isolated or allowed to react slowly with excess of thiol to give the corresponding alcohol **3**. It is usually more expedient to reduce the hydroperoxide by addition of a phosphine or a phosphite. This procedure suffers from the fact that it involves up to three different phases and several reagents which have to react with each other in a given order. Reproducibility, especially on a small scale, is thus difficult to achieve, and each case has to be optimised. An alternative, and more elegant reaction involves decomposing the N-hydroxythiopyridone ester **1** in the presence of tris(phenylthio)antimony under air.[5] This method is convenient for small scale work but the antimony reagent is sensitive to water and its hydrolysis liberates thiophenol which is detrimental to the efficiency and reproducibility of the process.[6] We now wish to report an improved variant of the first approach where many of the complicating factors which have so far hampered its utility as a synthetic tool have been circumvented.

N-hydroxythiopyridone esters **1** are quite sensitive to visible light, so that production of radicals can exceed the amount of oxygen present in solution. Moreover, these derivatives are powerful acylating agents (they are really "activated esters" and their ionic chemistry is more akin to that of anhydrides than to that of esters) and acylation of the thiol (or simple hydrolysis by adventitious water) represents a serious undesirable side reaction. Attempting to produce the radicals at a slower rate or operating under more dilute conditions increases the chances of destroying the thiohydroxamate ester by an ionic pathway. We therefore turned to esters **4** derived from N-hydroxy-4-methyl-2-thiazolinethione instead of those made from N-hydroxy-2-thiopyridone (Scheme 2). In earlier studies,[7] these readily available compounds were found to be much less sensitive to visible light and significantly more robust towards hydrolysis. This should allow a slow generation of radicals without undue ionic side reactions. For this particular purpose therefore, this family of thiohydroxamate esters appeared *a priori* better suited.

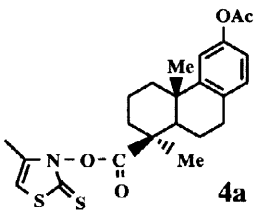
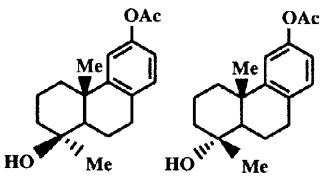
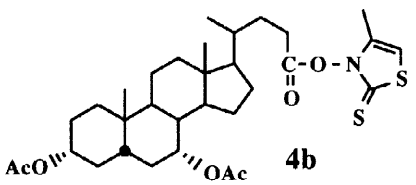
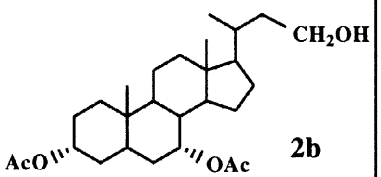
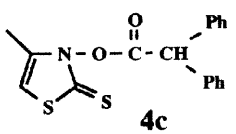
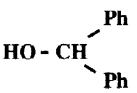
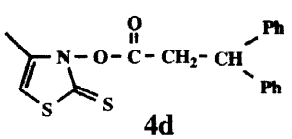
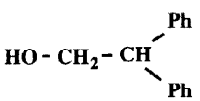
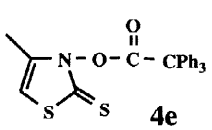
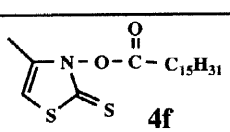
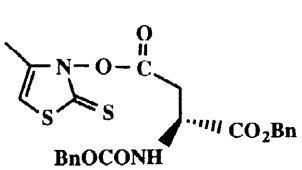
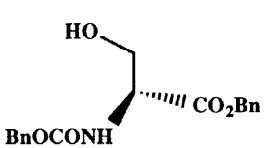


Scheme 2

Indeed, mere stirring under air or oxygen of a solution of esters **4** in the presence of *tert*-dodecanethiol (which is much less volatile and infinitely more tolerable than *tert*-butanethiol as far as stench is concerned) in toluene followed by reduction of the intermediate hydroperoxide with triphenylphosphine did bring about the desired transformation. However, reaction times were generally too long (1-2 days), indicating that initiation by spontaneous aerial oxidation of the thiol was clearly not very efficient; we therefore resorted to irradiation with visible light as a practical expedient. Our results on a variety of carboxylic acids are collected in the table.

These reactions have not been optimised but the following general observations can be made. Triphenyl phosphine proved to be the best reducing agent for the intermediate hydroperoxide in terms of efficacy and ease of removal. Attempts to decompose the peroxide by simply heating in the presence of the thiol were on the whole not satisfactory. Nor was the replacement of *tert*-dodecanethiol by the hydrochloride of 2-dimethylamino ethanethiol. The latter appeared attractive since it could be removed by extraction into water. Finally, stirring under air or under an atmosphere of pure oxygen gave similar results.

Table: Decomposition of N-hydroxy-2-thiazolinethione esters under air or oxygen.

Esters	Nor-alcohols	Yield
 4a	 2a (4βOH) 2a (4αOH)	57% (24% + 33%)
 4b	 2b	60%
 4c	 2c	67%
 4d	 2d	72%
 4e	HO-CPh$_3$ 2e	84%
 4f	HO-C$_{15}$H$_{31}$ 2f	80%
 4g	 2g	70%

In summary, this simple, practical procedure avoids the use of organo-antimony compounds employed in earlier methods. The very mild conditions should make it compatible with most aliphatic and alicyclic carboxylic acids.

Experimental section :

Melting points were determined with a Reichert hot stage apparatus and are uncorrected. IR spectra were recorded as neat films on a Nicolet 205 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on Brucker AC 200, AC 250 or AM 300 spectrometers as solutions in $CDCl_3$ with tetramethylsilane as internal standard (δ ppm). Mass spectra were recorded on MS 50 (electron impact), MS 9 (chemical ionisation) or MS 80 (high resolution) spectrometers. Matrex 60 (35-70 μm) silica gel was used for column chromatography. Solvents and reagents were purified according to standard laboratory techniques.

Esters **4a-g** derived from N-hydroxy-4-methyl-2-thiazolinethione were prepared as described earlier in the literature[7] and in most cases used without further purification.

3-[1,2,3,4,4a,9,10,10a-Octahydro-6-acetoxy-1,4a-dimethyl(1S,1α,4aα,10aβ)-1-phen-anthrenecarboxy]-4-methylthiazol-2(3H)-thione ***4a.***

Ester **4a** was purified on a short silica gel column (heptane-ethyl acetate: 1-1) to yield white crystals (75%). ^{1}H NMR (200 MHz) δppm 7.3-6.7 (m, 3H, Ph), 6.2 (s, 1H, *CH*=C), 3.1-2.5 (m, 2H), 2.3 (s, 3H, CO*CH*$_3$), 2.2 (s, 3H, *CH*$_3$), 1.65, 1.3 (2s, 6H, 2 *CH*$_3$). IR (nujol, ν_{max}) 1793, 1750 cm^{-1}. Mp 129°C (ethyl acetate-heptane). Anal. Calcd for $C_{23}H_{27}NO_4S_2$ C(62.00), H(6.11), N(3.14), S(14.39); found C(61.95), H(6.22), N(3.06), S(14.03). $[\alpha]_D^{20}$ = + 22 (c = 1.1, $CHCl_3$).

3-(3α, 7α–Diacetoxy-5β-cholanoxy-)-4-methylthiazol-2(3H)-thione ***4b.***

Ester **4b** was purified on a short silica gel column (heptane-ethyl acetate: 6-4) to give a white powder (70%). ^{1}H NMR (250 MHz, $CDCl_3$) δppm 6.2 (s, 1H, C*H*=C), 4.9 (m, 1H, C*H*OAc), 4.6 (m, 1H, C*H*OAc), 2.8-2.5 (m, 2H, C*H*$_2$), 2.1 (s, 3H, *CH*$_3$), 2.05, 2.09 (2s, 6H, 2 CO*CH*$_3$), 1.9-1.1 (m, 24H, C*H*, C*H*$_2$), 0.9, 0.6 (2s, 9H, 3 C*H*$_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δppm 170.7, 170.5, 170.4 (*C*O) ; 137 (C*H*=*C*CH$_3$), 102 (*C*H=CCH$_3$), 74.2, 71.3 (*C*HOAc), 55.8, 50.5 (*C*H), 42.9 (*C*), 41.1 (*C*H), 39.6 (*C*H$_2$), 38.1, 35.3 (*C*H), 35.0, 34.8 (*C*H$_2$), 34.2 (*C*H), 31.4, 30.8, 28.5, 28.1, 26.9, 23.7 (*C*H$_2$), 22.8, 21.7, 21.6 (*C*H$_3$), 20.8 (*C*H$_2$) 18.3, 13.4, 11.8 (*C*H$_3$). IR (νmax, nujol) 1813, 1728 cm^{-1}. MS (F.A.B., m/z) 606 (MH^+). Anal. Calcd for $C_{32}H_{47}NO_6S_2$ C(63.44), H(7.82), N(2.31); found C(63.51), H(7.82), N(2.12). $[a]_D^{20}$ = + 14.7 (c = 1.08; $CHCl_3$).

General procedure for the preparation of nor-alcohols.

A solution of esters **4a-g** (0.02 or 0.03 M) in toluene containing *tert*-dodecanethiol (4 eq.) was stirred vigorously and irradiated under an oxygen atmosphere using a Xenophot lamp (100 W). After stirring at room temperature for 30-120 min, triphenylphosphine (1.5 eq.) was added and the mixture stirred for a

few minutes. Evaporation of the solvent and purification of the residue by chromatography on a silica gel column gave the desired nor-alcohol. Alternatively, the ester can be kept under a neon light for 12-48 hrs before addition of the phosphine and identical workup. Nor-alcohols **2c**, **2d**, **2e**, **2f**, and protected serine derivative **2g**[8] are known compounds (the first four are commercially available) and were easily identified and characterised by comparison.

1,2,3,4,4a,9,10,10a-Octahydro-6-acetoxy-1,4a-dimethyl-1hydroxy- (1S or 1R,1α,4aα, 10aβ) phenanthrene ***2a***.

The reaction mixture was purified on a silica gel column (heptane-ethyl acetate: 1-1) to yield the oily mixture of nor alcohols **2a**.(57%).

Isomer **2a (4α-OH)** (24%). ^{1}H NMR (250 MHz) δppm 7.1-6.7 (m, 3H, Ph), 3.1-2.8 (m, 2H), 2.3 (s, 3H, CO*CH*$_3$), 2.2-1.35 (m, 9H, *CH*, CH$_2$), 1.3 (s, 3H, *CH*$_3$), 1.25 (s, 3H, *CH*$_3$). ^{13}C NMR (62.5 MHz, CDCl$_3$) δppm 150.8, 148.7, 132.6, 129.8, 118.5, 117.1 (*C*Ph), 72.2 (*C*OH), 48.3 (*C*H$_2$),40.7 (*C*CH$_3$), 38.1, 37.6, (*C*H$_2$), 30.8 (*C*H), 28.7 (*C*H$_2$), 24.3 (CO*C*H$_3$), 21.2 (*C*H$_2$), 18.4, 17.8 (*C*H$_3$). IR (nujol, ν$_{max}$) 3417, 1755 cm^{-1}. Mp 180-200°C (ether-pentane). Anal. Calcd for C$_{18}$H$_{24}$O$_3$ C(74.97), H(8.39); found C(74.63), H(8.39).

Isomer **2a (4β-OH)** (33%). ^{1}H NMR (250 MHz, CDCl$_3$) δppm 7.1-6.7 (m, 3H, Ph), 3.1-2.7 (m, 2H, C*H*$_2$), 2.25 (s, 3H, COC*H*$_3$), 2.2-1.3 (m, 9H, C*H*, C*H*$_2$), 1.2 (1s, 1H, C*H*$_3$), 1.15 (1s, 3H, C*H*$_3$). ^{13}C NMR (62.5 MHz, CDCl$_3$) δppm 170 (*C*OCH$_3$), 150.3, 148.7, 132.7, 130, 118.7, 117.5 (*C*Ph), 72.4 (*C*OH), 52 (*C*H$_2$), 42.6 (*C*CH$_3$), 38.6, 37.9 (*C*H$_2$), 29.7 (*C*H), 24.4 (CO*C*H$_3$), 22.9, 21.2 (*C*H$_2$), 20.4, 17.8 (*C*H$_3$). IR (neat, νmax) 3417 cm^{-1} (OH) ; 1755 cm^{-1} (*CO*CH$_3$).

3α,7α-Diacetoxy-23-hydroxy-24 nor-5β-cholane ***2b***.

The reaction mixture was purified on a silica gel column (ether-pentane : 70-30) to yield the nor alcohol **2b**.as a white powder (60%). ^{1}H NMR (250MHz, CDCl$_3$) δppm 4.9 (m, 1H, C*H*OAc), 4.6 (m, 1H, C*H*OAc), 3.65 (m, 2H, C*H*$_2$OH), 2.09, 2.05 (2s, 6H, 2 COC*H*$_3$), 2-1.05 (m, 24H, *CH*, *CH*$_2$), 1, 0.98, 0.7 (3s, 9H, 3 C*H*$_3$). ^{13}C NMR (62.5 MHz, CDCl$_3$) δppm 170.6 (*C*OCH$_3$), 74.2, 71.3 (*C*HOAc), 60.9 (*C*H$_2$OH), 56.5, 50.5 (*C*H), 42.9 (*C*), 41.0 (*C*H), 39.6, 39.0 (*C*H$_2$), 38.0 (*C*H), 35.0, 34.7 (*C*H$_2$), 34.2, 33.0 (*C*H) 31.4, 28.4, 26.9, 23.7 (*C*H$_2$), 22.8, 21.7, 21.6 (C*H*$_3$), 20.7 (*C*H$_2$), 18.9, 11.7 (C*H*$_3$)). IR (νmax) 3451, 1728 cm^{-1}. MS (CI., m/z) 449 (MH$^+$). Anal. Calcd for C$_{27}$H$_{44}$O$_5$ C(72.28), H(9.89); found C(72.25), H(9.84). [a]$_D^{20}$ = + 17 (c = 1.1; CHCl$_3$).

References.

1. The conversion of a carboxylic acid into the nor-alcohol using ionic reactions is usually a multistep procedure. One example, which proceeds via the nor-aldehyde or ketone, is the Barbier-Wieland degradation protocol, used in the early transformation of bile acids into pregnane derivatives: Fieser, L. F.; Fieser, M. *Steroids* ; Reinhold Publishing Corp.: New York, 1959
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Coda: Shortly after this manuscript was submitted, we were plunged into sorrow by the sudden and unwelcome death of Professor Sir Derek Barton. We had the privilege of working under his guidance, and enjoyed his kindness and warm friendship for many years. He constantly gave us help, advice, words of encouragement, and allowed us to benefit from his unbelievably vast knowledge of chemistry. His untimely departure leaves a large void in our hearts; we shall miss him very much.