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The Invention of Radical Reactions. Part XXV. A Convenient Method for the Synthesis of the Acyl Derivatives of *N*-Hydroxypyridine-2-thione

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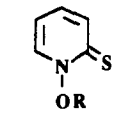
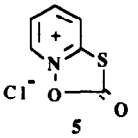
Abstract: *Treatment of the readily available di-N-oxide- of 2-thiopyridine disulfide* **6** *with tributylphosphine in the presence of a carboxylic acid provides a convenient and high yielding synthesis of the acyl derivatives* **2** *of N-hydroxy-2-thio-pyridone. Application of this procedure to the acids* **17** *and* **18** *gave, after irradiation in the presence of t-butylthiol, the desired decarboxylated derivatives in high (>90%) yield.*

The acyl derivatives of thiohydroxamic acids are a convenient source of carbon radicals[1,2]. The most commonly used compound is *N*-hydroxy-2-thiopyridone **1** which, if purchased as the aqueous solution of the sodium salt, is inexpensive[3]. These acyl derivatives **2** are also known as PTOC [((1H)-pyridine-2-thione) oxycarbonyl] esters[4] or Barton esters. The PTOC carbamates **3** have been used extensively by Newcomb[5] for generation of nitrogen radicals of various kinds. Similarly a number of oxygen based radicals have been obtained expeditiously[6].

The acyl derivatives **2** are prepared from the appropriate acid **4** through (a) the acid chloride, (b) the use of an appropriate carbodiimide, (c) the formation of the mixed anhydride with isobutyl chloroformate and a suitable base (d) the use of the crystalline salt **5** with loss of carbon dioxide from the intermediate pyrocarbonate. Method (c) has been especially useful for peptide[7] and nucleoside[8] manipulation (Scheme 1).



1 R = H 1a R = Na^+
2 R = R^1CO
3 R = NR^1R^2-CO



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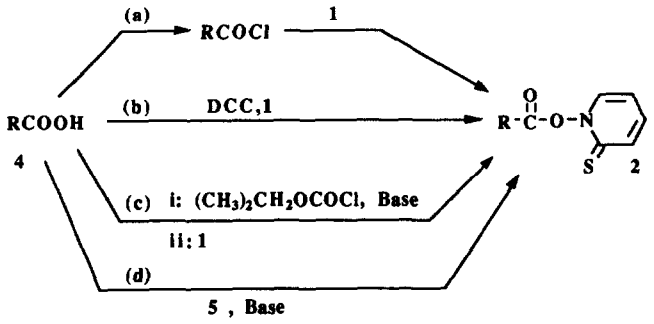
Scheme 1



Here we report a new procedure for the preparation of the acyl derivatives **2**. The thiopyridone **1** is easily oxidized by hydrogen peroxide to the disulfide[9] **6**. With tributylphosphine and the appropriate carboxylic acid **4** in CH_2Cl_2 at 0°C under argon the disulfide **6** gave the desired acyl derivatives **2** in high yield (Scheme 2). Table 1 shows the isolated yields of the acyl derivatives for typical primary, secondary, and tertiary acids.

Scheme 2

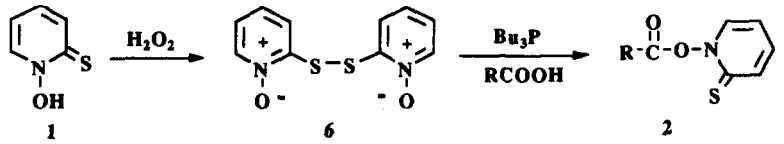
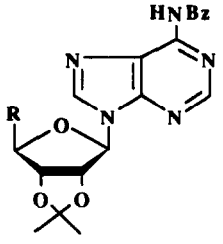


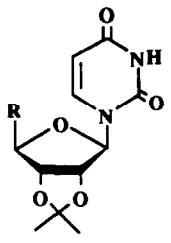
Table 1

	Entry	Ester 2	Yield
4a R- $PhCH_2CH_2$	1	2a	92%
4b R- Cyclohexyl	2	2b	86%
4c R- 1-Adamantyl	3	2c	84%

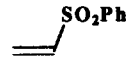
More importantly the adenosine derivative[8,10] **7** was readily converted to its *N*-hydroxy-2-thiopyridone derivative, addition of phenyl vinyl sulfone **13** and irradiation with two tungsten lamps at 10-15°C for 30 min, afforded the known adduct **9** in satisfactory isolated yield (78%). Similarly the corresponding acid[11] **10**, derived from uridine, gave the adduct **12** in good yield (95%). The addition of the esters of adenosine and uridine prepared by the action of disulfides in the presence of triphenylphosphine to olefin amide[10] **14** gave the addition products **15** and **16** in 71% and 78% yield respectively. The use of tributylphosphine instead of triphenylphosphine makes difficult the purification of compounds **15** and **16** contaminated by tributylphosphine oxide. In these experiments the intermediate acyl derivatives were not isolated due to their instability. This is our common practice for the manipulation of peptides and nucleosides. The good yield of radical addition products formed shows that the by-product, which is, *N*-hydroxy-2-thiopyridone **1** does not interfere in the reaction. Its non-radical chemistry is relatively slow[12]. The mechanism for the formation of **2** is assumed to be as in Scheme 3.



7 R = COOH
8 R = COOX
9 R = $CH_2CHY—SO_2Ph$
Bz = COC_6H_6



10 R = COOH
11 R = COOX
12 R = $CH_2CHY—SO_2Ph$



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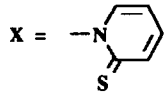
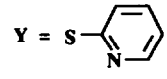
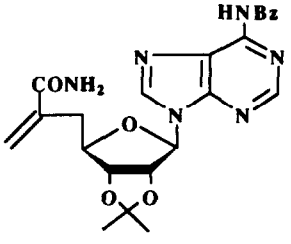
X = 

Y = 



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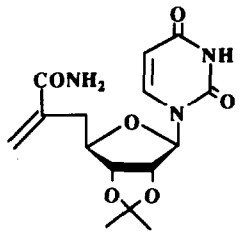

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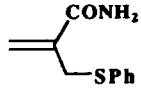

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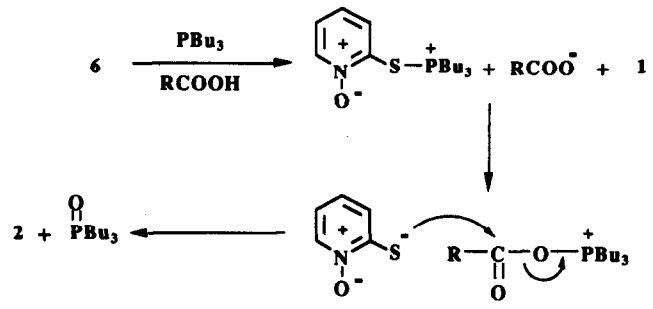
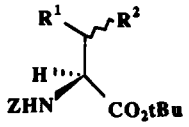
Scheme 3



Recently Baldwin[13] reported that two acids, **17** and **18**, were decarboxylated inefficiently (38% and 28%) using the standard derivatives **2**. In our experience the radical chemistry of **2** was always satisfactory, but, if care is not taken to exclude all moisture, the yield of **2** may be low. The new method of synthesis of **2** is self drying, as any water is converted to tributylphosphine oxide. We decided, therefore, to look at acids **17** and **18**. Again application of our procedure using tributylphosphine in the presence of the t-butylthiol and irradiation gave the desired decarboxylated acids **21** and **22** in 94% and 95% respectively. Thus, as we suspected, the traditional radical chemistry was as satisfactory as ever and the problem was in the synthesis of the Barton ester.



17 R^1= $PhCH_2$, R^2= COOH

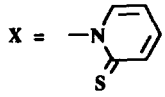
18 R^1= $CH_2{=}CH{-}CH_2$, R^2= COOH

19 R^1= $PhCH_2$, R^2= COOX

20 R^1= $CH_2{=}CH{-}CH_2$, R^2= COOX

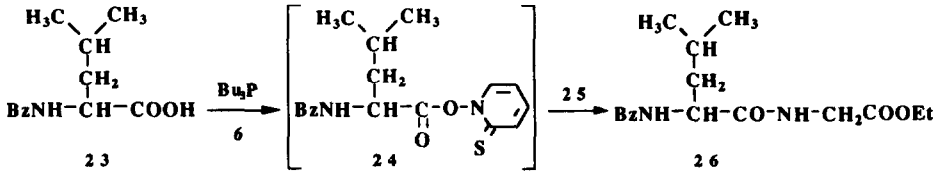
21 R^1= $PhCH_2$, R^2= H

22 R^1= $CH_2{=}CH{-}CH_2$, R^2= H

X = 

Finally, the reaction was applied to peptide synthesis. The target benzoyl-L-leucylglycine ethyl ester **26** was chosen as a model for the study of racemization. We used the Young test, which is known to be the most sensitive for the detection of racemization[14]. Thus, the benzoyl-L-leucine **23** was converted to its *N*-hydroxy-

2-thiopyridone derivative **24**, which was treated with glycine ethyl ester **25** to give the dipeptide **26** in 90% yield. The value of the optical rotation measured $[\alpha]_D^{20} = 0.0°$ showed complete racemization.



EXPERIMENTAL

^{1}H N.M.R. spectra were recorded at 200 MHz using either a Varian XL-200E or Gemini-200 spectrometer for solution in deuteriochloroform. Chemical shifts are in ppm with respect to internal Me_4Si. Infrared spectra (IR) were measured with a Perkin-Elmer 881 spectrometer. Melting points were determined using a Reicher apparatus and are uncorrected. Column chromatography was carried out on silica gel 60 (230-400) from Aldrich Chemical Co. TLC analysis was performed on thin layer analytical plates 60F254 (Merck). Mass spectra (MS) were recorded on an AEI MS50, AEI M59, and Kratos MS80 (for F.A.B. spectra). Elementary analysis was carried out at the Institut de Chimie des Substances Naturelles, Gif-Sur-Yvette.

General Procedure for the Preparation of *N*-Hydroxy-2-thiopyridone Acyl Derivatives 2:

(Note: Compounds of this type are somewhat sensitive to laboratory lighting. It is advisable to cover reaction flask, chromatography column etc. with aluminum foil).

To a solution of the carboxylic acid **4** (3 mmol) and 2,2'-dithiodipyridine-1,1'-dioxide (3.3 mmol, 0.832 g) in dry CH_2Cl_2.(15 ml) was added tributylphosphine (3.3 mmol, 0.822 ml) under argon at 0° C. The mixture was stirred at room temperature for 30 min, the yellow solution was subjected directly to flash chromatography using CH_2Cl_2 as eluant to give the esters **2**, which crystallized from hexane/CH_2Cl_2. Acyl derivatives **2a**, **2b** and **2c** were prepared and characterized as in the literature.[15,16,17]

(5',6'-Dideoxy-6'-phenylsulfonyl-2',3'-O-isopropylidene-6'-thio-(2'-pyridyl)-β-*D*-*ribo*-hexofuranosyl)-9-N^6-benzoyl-adenine 9:

To a solution of adenosine acid **7** (0.5 mmol, 213 mg) and 2,2'-dithiodipyridine-1,1'-dioxide (0.6 mmol, 152 mg) in dry CH_2Cl_2 (7 ml) was added under argon tributylphosphine (0.6 mmol, 0.152 ml). The mixture was stirred at room temperature for 1h. Phenyl vinyl sulfone (2.5 mmol, 0.420 g) was added and the mixture was irradiated with two tungsten lamps (120W) at 10°-15°C for 30 min. The mixture was diluted with CH_2Cl_2 (50 ml) and washed with saturated $NaHCO_3$ (30 ml), water (30 ml), saturated NaCl (30 ml) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was subjected to flash chromatography using ethyl acetate-hexane (7-3) as eluant to give the addition product **9** as a white crystalline compound. Yield 257 mg (78%). M.p.: 105-108°C (CH_2Cl_2-pentane); M.S: (F.A.B.) m/e: 659 $(MH)^+$, 420

(MH-Base)$^+$, 240 (Base+H)$^+$; Anal. ($C_{32}H_{30}N_6O_6S_2$), Calcd C(58.35), H(4.55), N(12.76), S(9.72). Found C(58.30), H(4.82), N(12.64), S(9.66).

(5',6'-Dideoxy-6'-phenylsulfonyl-2',3'-O-isopropylidene-6'-thio-(2'-pyridyl)-β-*D-ribo*-hexofuranosyl)-1-uracil 12:

This compound was prepared in an identical manner to **9** using uridine acid **10** (0.5 mmol, 0.149g). Flash chromatography using ethyl acetate-hexane (7-3) gave the addition product **12** as a white crystalline compound. Yield 253 mg (95%). M.p: 106-108 0°C (CH_2Cl_2-hexane).; ν_{max} (nujol): 1685, 1580, 1420, 1310, 1270, 1150, 1080 cm^{-1} ; MS (IC) m/e: 532(MH)$^+$; Anal. ($C_{24}H_{25}N_3O_7S_2$), Calcd C(54.23), H(4.70), N(7.90), S(12.05). Found C(54.06), H(4.67), N(8.15), S(12.23).

(5',6',7'-trideoxy-6'-carboxamide-2',3'-O-isopropylidene-β-*D-ribo*-hexofuranosyl)-9-N^6-benzoyl-adenine 15:

To a solution of adenosine acid **7** (0.5 mmol, 213 mg) and 2,2'-dithiodipyridine-1,1'-dioxide (0.6 mmol, 152 mg) in dry CH_2Cl_2 (7 ml) was added under argon triphenylphosphine (0.6 mmol, 158 mg). The mixture was stirred at room temperature for 1h. Olefinic amide **14** (2.5 mmol, 0.483 g) was added and the mixture was irradiated with two tungsten lamps (120W) at 10°-15°C for 30 min.The mixture was diluted with CH_2Cl_2 (100 ml) and washed with saturated $NaHCO_3$ (50 ml), water (50 ml), saturated NaCl (50 ml) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was subjected to flash chromatography using ethyl acetate-MeOH (9.5-0.5) as eluant to give the addition product **15** as a white crystalline compound.Yield 165 mg (71%).M.p.: 110-114°C (CH_2Cl_2-pentane); $[\alpha]_D^{20}$= +4.8° (c= 0.5; $CHCl_3$); MS: (C.I.) m/e: 465 (MH)$^+$, 240 (Base+H)$^+$; Anal. ($C_{23}H_{24}N_6O_5$), Calcd C(59.48), H(5.17), N(18.10). Found C(59.19), H(5.18), N(17.95).; ν_{max} (nujol): 1671, 1611, 1582, 1254, 1212, 1093 cm^{-1}.; δ_H: 8.88 (s, 1H, H2), 8.15 (s, 1H, H8), 8.04-7.75 (m, 5H, Ph), 6.11 (s, 1H, H1'), 6.06 (sl, 2H, $CONH_2$), 5.76 (s, 1H, H7'), 5.53 (d, 1H, J2',3'= 6Hz, H2'), 5.36 (s, 1H, H7"), 4.96 (dd, 1H, J3',2'=6Hz,J3',4'=3Hz, H3'), 4.46 (td, 1H, J4',3'=3Hz, J4',5'=7Hz, H4'), 2.73 (d, 2H, J5',4'=7Hz, H5', H5"), 1.60, 1.38 (2s, 6H, CMe_2).

(5',6',7'-Trideoxy-6'-carboxamide-2',3'-O-isopropylidene-β-*D-ribo*-hexofuranosyl)-1-uracil 16:

This compound was prepared in an identical manner to **15** using uridine acid **10** (0.5mmol, 0.149g). Flash chromatography using ethyl acetate-hexane (7-3) gave the addition product **16** as a white crystalline compound.Yield 132 mg (78%).M.p.: 106-108°C (CH_2Cl_2-pentane); $[\alpha]_D^{20}$= +32° (c= 0.5; $CHCl_3$); MS: (C.I.) m/e: 338 (MH)$^+$, 113 (Base+H)$^+$; Anal. ($C_{15}H_{19}N_3O_6$), Calcd C(53.41), H(5.63), N(12.46). Found C(53.30), H(5.73), N(12.27).; ν_{max} (nujol): 1715, 1700, 1690, 1680 cm^{-1}.; δ_H: 10.33 (s, 1H, NH), 7.30 (d, 1H, J6,5=8Hz, H6), 6.36 (sl, 2H, $CONH_2$), 5.90 (s, 1H, H7'), 5.73 (dd, 1H, J5,6=8Hz, H5), 5.56 (d, 1H, J1',2'=1Hz, H1'), 5.53 (s, 1H, H7"), 5.05 (dd, 1H, J2',1'=1Hz, J2',3'=6Hz, H2'), 4.75(dd, 1H, J3',2'=6Hz, J3',4'=5Hz, H3'), 4.26 (m, 1H, J4',3'=5Hz, J4',5'=7Hz, J4',5"=6Hz, H4'), 2.76 (m, 2H, H5', H5"), 1.55, and 1.33 (2s, 6H, CMe_2).

t-Butyl N-Z-(S)-homophenylalanine 21:

To a solution of acid **17** (1 mmol, 0.413 g) and 2,2'-dithiodipyridine-1,1'-dioxide (1.2 mmol, 0.305 g) in dry CH_2Cl_2 (10 ml) was added under argon tributylphosphine (1.2 mmol, 0.314 ml) at 0°C.The mixture was stirred for 30 min at room temperature. 2-methyl-2-propanethiol (1 ml) was added, and the mixture was irradiated with two tungsten lamps (120 W) at 10-15°C for 30 min.The mixture was diluted with ether (100 ml), and washed with saturated $NaHCO_3$ (50 ml), water (50 ml), saturated NaCl (50 ml), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue subjected to flash chromatography (10% ethyl acetate/hexane), giving **21** as a colorless oil which slowly crystallized. Yield 347 mg (94%).$[\alpha]_D^{25}$=+15.0° (c 1.2 $CHCl_3$) lit[13] $[\alpha]_D^{20}$=12.0°.; ν_{max} (neat): 1730, 1714 cm^{-1}.; MS (CI) m/e: 370 (MH)$^+$, 314 (MH-56)$^+$.; δ_H: 7.31-7.12 (m, 10H, 2 Ar), 5.31 (d, 1H, J 7.5 Hz, NH), 5.08 (s, 2H, O$\underline{CH_2}$Ph),

4.3 (dd, 1H, J 12.5 and 6.25 Hz, NCH), 2.65 (m, 2H, $PhCH_2CH_2$), 2.15-1.9 (m, 2H, $CHCH_2$), 1.46 (s, 9H, $OC(CH_3)_3$).

t-Butyl 2-benzyloxycarbonylamino-(2S)-5-hexenoate 22:

Compound **22** was prepared in an identical manner to **21** above using acid **18** (1 mmol, 0.303 g). Flash chromatography (10% ethyl acetate/hexane) gave **22**[13] as a colorless oil. Yield 303 mg (95%). ν_{max} (neat): 1734, 1713 cm^{-1}.; MS (CI) m/e: 320 $(MH)^+$, 264 $(MH-56)^+$.; dH: 7.36 (s, 5H, Ar), 5.81 (m,1H, J 16 and 7.5 Hz, $CH=CH_2$), 5.36 (d, 1H, J 7.5 Hz, NH), 5.11 (s, 2H, OCH_2Ph), 5.05 (dd, 1H, J 16 and 1.5 Hz, C=CH), 4.98 (d, 1H, J 7.5 Hz, C=CH), 4.29 (dd, 1H, J 12.5 and 7.5 Hz, NCH), 2.11-1.6 (m, 4H, CH_2CH_2), 1.45 (s, 9H, $OC(CH_3)_3$).

Benzoyl-DL-leucylglycine ethylester 26:

To a solution of acid **23** (4 mmol, 0.940 g) and 2,2'-Dithiodipyridine-1,1'-dioxide (4.4 mmol, 1.109 g) in dry CH_2Cl_2 (24 ml) was added under argon tributylphosphine (4.4 mmol, 1.1ml) at 0°C.The mixture was stirred for 30 min at room temperature. Glycine ethyl ester **25** (4.8 mmol, 0.495 g) was added, and the mixture was Stirred for 15 min at 0°C. The mixture was diluted with CH_2Cl_2 (100 ml), and washed with N HCl (50ml), water (50ml), saturated $NaHCO_3$ (50 ml), water (50 ml), saturated NaCl (50 ml), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue subjected to flash chromatography (50% ethyl acetate/hexane), giving **26** as a white crystalline compound. Yield 1.155 g (90%). M.p: 142-144°C (ethyl acetate-pentane), lit[14]: 144.5-145.5°C.; $[\alpha]_D^{20}$ = 0.0° (c=3.2 EtOH). This value of specific rotation corresponds[14] to a mixture of 50% L and 50% D isomer.

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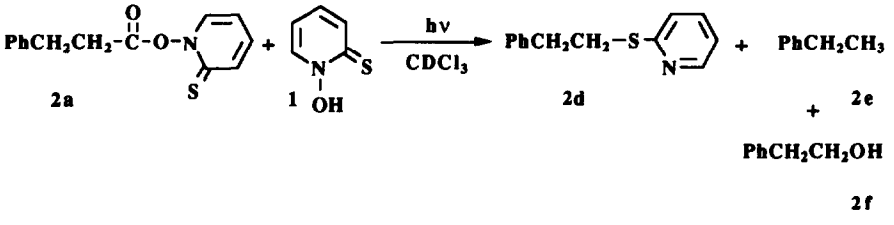
12. The acyl derivative **2a** (0.5 mmol, 129.5 mg), and *N*-hydroxy-2-thiopyridone **1** (0.5 mmol, 63.5 mg) in $CDCl_3$ (3 ml) were irradiated with a tungsten lamp (250 W) under argon for 1 hour at 20°C. Analysis of the mixture by N M R. showed the formation of 2-(β-phenethylthio)pyridine (70%), ethylbenzene (20%), and β-phenylethyl alcohol (10%). Thus **1** is a minor source of hydrogen atom transfer, but it cannot compete in this reaction with t-butylthiol. Also it cannot compete with the thiocarbonyl group of **2** in reactions with relatively electrophilic radicals resulting from addition to olefins like **13**, **14**, **15**, and **16**. The β-phenylethyl alcohol may come from an attack of the radical on the oxygen of compound **1**. When 5 equivalents of **1** were employed 2-(β-phenethylthio)pyridine (55%), ethylbenzene (38%), and the β-phenylethyl alcohol (7%) were obtained.



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