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THE INVENTION OF RADICAL REACTIONS PART XVIII. A CONVENIENT SOLUTION TO THE 1-CARBON PROBLEM ($R\text{-}CO_2H \longrightarrow R\text{-}^{13}CO_2H$)*

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Abstract - Radicals generated by photolysis (W light) of esters derived from N-hydroxy-2-thiopyridone react with electrophilic isocyanides 2a and (in the presence of trifluoracetic acid) 2b to give adducts of type 3. Convenient reaction procedures have been worked out to hydrolyse the adducts to amides of type 5, from which the original acid can be regenerated under mild conditions. The three important acids oleic, linoleic and arachidonic have all given smooth reactions. In suitable examples, quantitative evolution of carbon dioxide and incorporation of ^{13}C without dilution have been demonstrated. This reaction sequence will be useful for the labelling in the carboxyl group of prostaglandins, leukotrienes, and the side chain carboxyls of peptides.

Carboxylic acids are an important class of biologically active Natural Products. Amongst these the prostaglandins[1] and leukotrienes[2] are of current interest as well as a multitude of small peptides and amino-acids.[3] The two former classes of compounds are sensitive to acidic and basic conditions and many react with oxygen under radical conditions. To our knowledge there is no convenient way to label the carboxyl group in these compounds with ^{13}C or ^{14}C, although such labelling would be very useful in biological experiments. We have called this the "one carbon" problem.

Recently there has been considerable progress in the use of the carboxyl group as a convenient source of "disciplined" radicals.[4,5] The most convenient modification of our use of thiohydroxamic esters as radical generators is the photolysis with tungsten light of compounds of type 1. The carbon radicals $R^{\bullet}$ which are formed can be intercepted by many radicophilic functional groups to give another radical which can again generate an $R^{\bullet}$ radical by reaction with the thiocarbonyl group of 1. The 2-thiopyridyl group which is thus added can be easily removed, or it can lend itself to further useful manipulation.[5,6]

We conceived that the radicals $R^{\bullet}$ generated from a carboxylic acid should be able to react with a suitable one carbon trap, which could then be converted back into the carboxyl function. The problem was to find a sufficiently reactive "one carbon" reagent which could be manipulated under very mild conditions. The sort of functionality present in (say) the leukotrienes means that a trivial solution like addition to acrylic acid, elimination to unsaturated acid and degradation back to starting acid[7] would be completely impractical.

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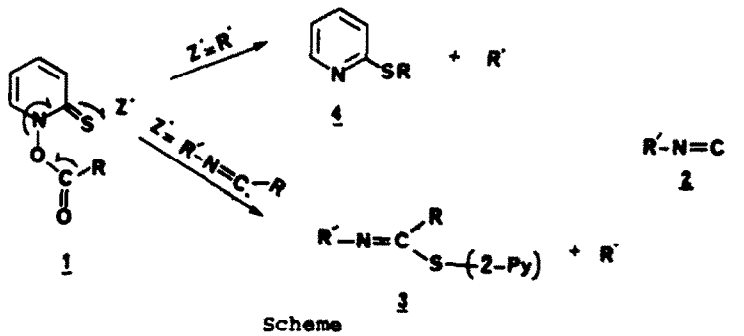
* This article is dedicated to our Publisher, Mr. Robert Maxwell on the occasion of his sixty-fifth anniversary. Salute Super-Max.

We considered two one carbon fragments: isocyanides and carbon monoxide. We could not find any addition to carbon monoxide, even at low temperature, nor could we add a radical to an ordinary isocyanide (cyclohexyl), the background rearrangement reaction being much faster. The recorded reaction with t-butyl isocyanide required rather special reaction conditions.[8]

Consideration of the Scheme for addition to an isocyanide 2 suggests that an electrophilic substituent should potentiate reactivity towards a nucleophilic radical R·



1 4 2 3

Scheme

Table 1: Preparation of N-Hydroxy-2-thiopyridone Esters 1

Entry	Ester 1[1]	Method	Yield (%)	Melting Point (°C) Recorded	lit.
1	1a	A	86	135	
2	1b	A	87	75	48-55 (dec)
3	1c	A	82	Oil	
4	1d	A	94	Oil	
5	1e	A	75	110	110
6	1f	A	71	83	
7	1g	B	68	113	
8	1h	A	90	Oil	
9	1i	A	85	166	165

A: Preparation of acid chloride from carboxylic acid 6 using oxalyl chloride and trace of DMF was followed by its reaction with N-hydroxy-2-thiopyridone in the presence of pyridine. B: Reaction of salt 7 with carboxylic acid 6 in the presence of Et_3N,i: Reference for esters 1h: 19, 1a: 18, 1i: 20.

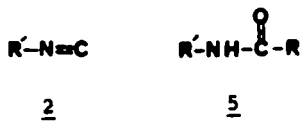
If the chain be carried in the usual way, then the product of the reaction would be 3. We report the synthesis of a number of thiohydroxamic esters of type 1 and of isocyanides 2 potentially reactive towards radicals.

The esters 1 were all but one prepared by the reaction of the acid chloride with N-hydroxy-2-thiopyridone in the usual way (Table 1). Of particular interest were the derivatives of oleic 1c, linoleic 1d and arachidonic 1h acids because these approach the kind of functionality found in the leukotrienes. There was no difficulty in the preparation or manipulation of any of the esters of Table 1.

The isocyanides listed in Table 2 were prepared by two standard methods. The appropriate amine was formylated and the derived formamide dehydrated by phosgene-triethylamine.[9] Alternatively the amine was treated with alkali and chloroform.[10]

The p-nitrophenyl isocyanide 2a was a stable crystalline compound and showed satisfactory radicophilicity. So also did 3-pyridyl isocyanide 2b in the presence of a little trifluoroacetic acid. However, this isocyanide polymerised when pure and so it was manipulated only in solution. The 2- and 4-pyridyl isomers polymerised even more easily and could not be used. The 4-quinaldine isocyanide 2d also could not be isolated, whereas the 3-quinoline derivative 2c and the p-dimethylaminophenyl isocyanide 2e could be obtained pure, but were not reactive enough towards radicals even on protonation. The data are presented semi-quantitatively in Table 1, which includes also data on the commercially available p-tolylsulfonylmethyl isocyanide (TOSMIC). The isonitriles 2a and 2b have the best compromise between reactivity towards radicals and stability.

The data recorded in Table 3 refer to experiments with ester 1a. The reaction product in the absence of trap is always the rearranged decarboxylation product 4a. In the presence of the isocyanides varying yields of the desired adduct 3a or of the corresponding amide 5a are obtained. The adducts of type 3a are readily hydrolysed even with water.



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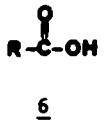

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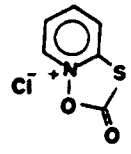

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1, 4, 6

a, R = $PhCH_2CH_2$
b, R = $CH_3(CH_2)_{14}$
c, R = cis-8-Heptadecenyl
d, R = cis-8,11-Heptadecadienyl
e, R = Cyclohexyl
f, R = $CH_3CH_2(CH_3)CH$
g, R = $(CH_3)_3C$
h, R = cis-4,7,10,13-Nonadecatetraenyl
i, R = 1-Adamantyl

2

2a, R' = p-$O_2NC_6H_4$
2b, R' = 3-Py
2c, R' = 3-Quinolyl
2d, R' = 4-Quinaldinyl
2e, R' = p-$(CH_3)_2NC_6H_4$
2f, R' = p-$CH_3C_6H_4SO_2CH_2$
2g, R' = Cyclohexyl

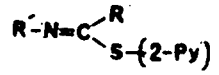
Table 2: Preparation of Isocyanides 2

Entry	Isocyanide 2[(1)]	Method	Yield (%)	Melting Point (°C) Recorded	lit.
1	2a	A	43	114-116	115-118
2	2a	B	84	114-116	
3	2b	A	30	(ii)	
4	2c	A	33	81-82	
5	2d	A	39	(ii)	
6	2e	A	45	59-60	

A: Amine was treated with $CHCl_3$/NaOH, B: Formamide prepared from p-nitro-aniline was reacted with $COCl_2$ in the presence of Et_3N. i: Reference for isocyanide 2a:22, 2b:23,24, 2e:23,25. ii: Polymerized upon removing the solvent and are not stabilized by base.[21]

1, 5

a, R = $PhCH_2CH_2$, R' = 3-Py
b, R = $CH_3(CH_2)_{14}$, R' = 3-Py
c, R = cis-8-Heptadecenyl, R' = 3-Py
d, R = cis-8,11-Heptadecandienyl
R' = 3-Py
e, R = Cyclohexyl, R' = 3-Py
f, R = $CH_3CH_2(CH_3)CH$, R' = 3-Py
g, R = $(CH_3)_3C$, R' = 3-Py
h, R = cis-4,7,10,13-Nonadeca-tetraenyl, R' = p-$O_2NC_6H_4$
i, R = $PhCH_2CH_2$, R' = p-$O_2NC_6H_4$
j, R = $CH_3(CH_2)_{14}$, R' = p-$O_2NC_6H_4$



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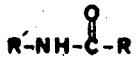

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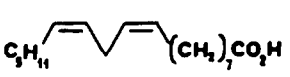
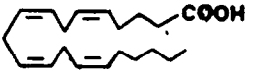


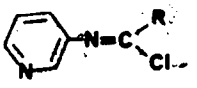
6d



6h

8, 9

a, R = $PhCH_2CH_2$
b, R = $CH_3(CH_2)_{14}$
c, R = cis-4,7,10,13-Nonadeca-tetraenyl



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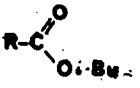

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Table 3: Reactivity of 2-Phenylethyl Radical Toward Isocyanides 2

Entry	Isocyanide 2 (mmol)	Reaction Conditions	Products (% Yield)
1	2a(5.0)	A; 28°C	3(30), 4(20), 5(50)
2	2b(5.5)	B; -15°C	3(80), 4(20)
3	2c(5.5)	B; -15°C	3(55), 4(35)
4	2a(5.0)	C; 25°C	4(65), 5(30)
5	2f(5.0)	A; 0°C	3(45), 4(55)
6	2g(15)	C; 0°C	4(80)

A: Inverse Addition, B: In presence of CF_3COOH, C: Neutral conditions

Taking precautions to eliminate water, a range of esters was photolysed in the presence of isocyanides 2a or 2b (Table 4). For all primary and secondary acids, the yields of adducts 3 were satisfactory. Even the t-butyl radical gave a significant yield. However the 1-adamantyl radical did not react at all.

All the adducts 3 based on 3-pyridyl isocyanide were readily converted to the corresponding amide 5 simply on treating with dioxane and water at room temperature. The adducts from the p-nitrophenyl isocyanide were likewise hydrolysed on silica gel chromatography.

Table 4: Addition of Alkyl Radicals to Isocyanides 2

Entry	Reactants	Temp. °C	Irradiation Time (min.)	Products[1] (% Yield)
1	1a, 2b	-15	10	3a(80), 4a(20)
2	1b, 2b	-15	10	3b(62), 4b(21)
3	1c, 2b	-10	15	3c(58), 4c(15)
4	1d, 2b	-10	15	3d(60), 4d(15)
5	1e, 2b	-15	25	3e(70)
6	1f, 2b	-15	25	3f(69), 4f(5)
7	1g, 2b	-15	30	3g(50), 4g(40)
8	1h, 2a	40	60	4h(15), 5h(35)
9	1a, 2a	28	60	4a(20), 5a(71)

(1) Reference for sulfides 4b and 4g: 20.

With the amides in hand, attention could be given to their hydrolysis. Clearly, ordinary acid or base hydrolysis[11] would not be applicable to leukotriene derivatives. Using amide 5a a mild procedure based on anion-CS_2 cleavage [12] was developed. Thus, amide 5a was treated with the lithium salt of hexamethydisilazane and then with carbon disulfide. This gave the corresponding thioacid which was converted into its O-trimethylsilyl derivative with the excess of hexamethyldisilazane.[13] Addition of phenylseleninic acid, as expected[14], converted the thiocarbonyl grouping to carbonyl and thus, addition of water, gave the required acid. If water was added before the addition of the phenylseleninic acid, the corresponding thiol acid was formed, readily converted by air, or by phenylseleninic acid, into the diacyldisulfide and not the free acid. Table 5 summarises the results obtained. The procedure was satisfactory for all primary acids. It gave less satisfactory results with a secondary acid and no acid was formed in the pivalic acid case. Since all the important, biologically relevant acids involved, including the side chain carboxyl groups in peptides, are primary the failure of the reaction in the tertiary case is not serious.

A second method was also developed involving an imino-chloride intermediate. Treatment of the amide 5a with PCl_5-pyridine gave the derived imino-chloride[15] (8) which on treatment with isobutanol and then water gave the isobutyl ester [16] (9). Mild base hydrolysis then afforded the acid. This was the best method for the p-nitrophenyl derivatives (Table 6). Good results were also obtained using phosgene-pyridine[17] and these conditions could be applied without difficulty to arachidonic acid.

Since we start with a carboxylic acid and convert it back to starting material, we thought it desirable to prove that we had really removed the CO_2. This was done in two experiments. Firstly, the amount of CO_2 evolved in the photolysis of ester 1a in the

presence of 3-pyridyl isocyanide 2b was shown by the barium carbonate method to be 97%. Secondly, the radical from ester 1a was allowed to react with isocyanide 2a which had been enriched in ^{13}C (7.5%). After purification, the amide 5a was obtained labelled on the amide carbon with ^{13}C (7.2%).

The manipulation of the sensitive arachidonic acid (6h) under conditions of radical generation and trapping is the most severe test for the methods developed in this paper. We have also examined the reactivity of the radical from arachidonic acid towards diphenyl diselenide. This afforded the expected derivative cis-4,7,10,13-nonadecatetraenylphenyl-selenide in good yield (72%).

Table 5: Hydrolysis of Thioimidates 3

Entry	Substrate	Hydrolysis to Amide 5, Time (hrs.)	Amide 5[(i)] (% Yield)	Acid 6 (% Yield)
1	3a	12	5a(90)	6a(65)
2	3b	12	5b(81)	6b(60)
3	3c	40	5c(93)	6c(51)
4	3d	40	5d(89)	6d(58)
5	3e	12	5e(95)	6e(63)
6	3f	36	5f(90)	6f(35)
7	3g[(ii)]			

(i) Reference for amide 5c: 26; 5g: 27. (ii) No amide was formed after 40 hrs.

Table 6: Hydrolysis of N-(p-Nitrophenyl)-amides

Entry	Amide	Method	Product (% Yield)
1	5h	B	6h(67)
2	5i	A	6a(85)
3	5i	B	6a(94)
4	5j	A	6b(90)

A: PCl_3, then successive treatment with pyridine, t-BuOH, 3N NaOH and H_2SO_4

B: $COCl_2$, then successive treatment with pyridine, t-BuOH, 3N NaOH and H_2SO_4

Experimental

N.M.R. spectra were recorded at 200 MHz with a Varian XL-200E spectrometer for solutions in deuteriochloroform. Chemical shifts are in ppm. with respect to internal $SiMe_4$. Ir spectra were measured with a Perkin-Elmer 881 spectrometer and U.V. spectra with a Beckmann DU-7 spectrometer. Electron impact (70 eV.) mass spectra were recorded on a Hewlett-Packard 5995C quadrupole gc-ms instrument. Exact mass measurements were carried out with a VG Analytical 705 high resolution double focusing magnetic sector mass spectrometer with attached VG Analytical 11/250J data system. Microanalyses were performed at the Center of Trace Characterization, Texas A&M University. Melting points are determined on a Kofler hot stage and are uncorrected. N-Hydroxypyridine-2-thione was prepared [28] from the 40% aqueous solution of its sodium salt (trade name: sodium omadine from the Olin Corp.).

General Procedure for Preparation of N-Hydroxy-2-thiopyridone Esters 1

Method A: A solution of the carboxylic acid (0.82 mmol) in dry benzene (2 ml) and DMF (1 drop) was treated with oxalyl chloride at room temperature. One hour after the evolution of gas had ceased, the solvent and excess oxalyl chloride were removed in vacuo. The N-hydroxypyridine-2-thione (109 mg; 0.86 mmol) in benzene (2 ml) was added dropwise followed by pyridine (0.07 ml; 0.86 mmol) in benzene (0.2 ml). The cooling bath was removed and the stirring was continued for 2 hrs. The reaction mixture was diluted with benzene, filtered and concentrated at reduced pressure. The residue was purified by chromatography on silica gel then the esters, when solid, were recrystallized from hexane/CH_2Cl_2 (Table 1).

Ester 1a ν (CH_2Cl_2) 1810, 1610 cm^{-1}; δ: 7.69 (1H,d), 7.55 (1H,d), 7.32-7.23 (5H,m), 7.19 (1H,t), 6.60 (1H,t), 3.19-3.11 (2H,m), 3.07-2.99 (2H,m).

Ester 1c ν (neat) 1810, 1610 cm^{-1}; δ: 7.68 (1H,d), 7.53 (1H,d), 7.27 (1H,t), 6.60 (1H,t), 5.31 (2H,t), 2.68 (2H,t), 2.00 (4H,m), 1.80 (2H,m), 1.31-1.24 (20H,m), 0.86 (3H,t).

Ester 1d ν (neat) 1807, 1608 cm^{-1}; δ:7.68 (1H,d), 7.53 (1H,d), 7.27 (1H,t), 6.60 (1H,t), 5.35 (4H,m), 2.76 (2H,t), 2.69 (2H,t), 2.04 (4H,m), 1.80 (2H,m), 1.40-1.23 (14H,m), 0.86 (3H,t).

Ester 1e ν (CH_2Cl_2) 1790, 1610 cm^{-1}; δ: 7.68 (1H,d), 7.53 (1H,d), 7.19 (1H,t), 6.62 (1H,t), 2.75 (1H,tt), 2.18 (2H,d), 1.90-1.63 (5H,m), 1.45-1.23 (3H,m).

Ester 1f ν (CH_2Cl_2) 1799, 1610 cm^{-1}; δ: 7.69 (1H,d), 7.53 (1H,d), 7.18 (1H,t), 6.61 (1H,t), 2.78 (1H,m), 1.89 (1H,m), 1.63 (1H,m), 1.37 (3H,d), 1.03 (3H,t).

Ester 1g ν (CH_2Cl_2) 1786, 1610 cm^{-1}; δ: 7.64 (1H,d), 7.49 (1H,d), 7.15 (1H,t), 6.60 (1H,t), 1.44 (9H,s).

Ester 1h ν (neat) 1807, 1608 cm^{-1}; δ:7.68 (1H,d), 7.53 (1H,d), 7.20 (1H,t), 6.61 (1H,t), 5.37 (8H,m), 2.81 (6H,m), 2.71 (2H,t), 2.21 (2H,m), 2.02 (2H,m), 1.89 (2H,m), 1.29 (6H,m), 0.87 (3H,t).

Method B: To a suspension of the salt 7 (1.02 g; 5.38 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise (at 0°C) pivalic acid (0.540 mg; 5.30 mmol) and triethylamine (1.11 ml; 7.9 mmol) as a solution in CH_2Cl_2 (10 ml). The reaction mixture was stirred at RT for 3 hrs., then diluted with CH_2Cl_2 (30 ml), washed with 10% aqueous $NaHCO_3$ then with water. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. The precipitate of 1g was recrystallized from Hexane/CH_2Cl_2 (Table 1).

General Procedure for the Preparation of the Isocyanides 2

Method A: To a well-stirred solution of the amine (26 mmol) in CH_2Cl_2 (15 ml) and $CHCl_3$ (2.5 ml) containing n-Bu_4NHSO_4 (0.9 g; 2.6 mmol) was added in one portion 50% aqueous NaOH (15 ml). The reaction mixture was stirred for 12 hrs., then diluted with water and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over $MgSO_4$ and concentrated at reduced pressure. Chromatography on silica gel (CH_2Cl_2: 2b, 2c, 2d; $CHCl_3$: 2e; Hexane/CH_2Cl_2 60/40: 2a) furnished the pure isonitrile 2 (See Table 2).

Method B: To formic acid (91%; 8 ml; 0.19 mole) cooled at 0°C, freshly distilled Ac_2O (6.8 ml; 72 mmol) was added. After stirring at RT for 1 hr. this solution was treated with p-nitroaniline (5 g; 36 mmol) and stirred overnight at RT. The reaction mixture was then treated with saturated aqueous K_2CO_3 until pH=8. The precipitate of formamide was collected by filtration, washed with cold water and dried under vacuum over P_2O_5. This compound was used in the next step without further purification: 5.5 g. (90%); mp: 184°C. ν(THF) 3249, 1709, 1598 cm^{-1}; δ:8.49 (1H,s); 8.24 (2H,d); 7.90 (2H,d); 7.52 (1H,s).

To a suspension of the formamide (2 g; 12 mmol) in dry CH_2Cl_2 (20 ml), dry NEt_3 was added (3.35 ml; 24 mmol). The reaction was cooled at 0-5°C and phosgene (1.20 g; 12.1 mmol) as a solution in dry CH_2Cl_2 was added dropwise. The cooling bath was removed and the mixture stirred overnight. After filtration, the solution was diluted with CH_2Cl_2, washed with brine and dried over $MgSO_4$. Concentration and purification by chromatography on silica gel (Hexane/CH_2Cl_2 60/40) allowed isolation of the pure isocyanide 2a: 1.6 g (90%).

4-Nitrophenyl isocyanide 2a ν (CH_2Cl_2) 2120 cm^{-1}; δ (^1H): 8.30 (2H,d), 7.56 (2H,d); δ (^{13}C): 169.7 (s), 147.5 (s), 127.5 (d), 125.1 (d).

3-Pyridyl isocyanide 2b ν (CH_2Cl_2) 2129 cm^{-1}; δ:8.68 (1H,s), 8.64 (1H,d), 7.69 (1H,d), 7.38 (1H,dd); UV (CH_2Cl_2) λmax: 228.5 (ϵ 5525), λmax: 267.5 (ϵ 3059). The concentration of 3-pyridyl isocyanide in the (CH_2Cl_2) solution could also be determined by comparison of $\nu_{N\equiv C}$ with a standard (CH_2Cl_2) solution of cyclohexyl isocyanide ($\nu_{N\equiv C}$: 2140 cm^{-1}). The 3-

pyridyl isocyanide could be kept for about a week in solution (0.35 mol/l) at -20°C under inert atmosphere.

3-Quinoline isocyanide 2c ν (CH_2Cl_2) 2133 cm^{-1}; δ: 8.85 (1H,s), 8.14 (1H,s), 8.11 (1H,d), 7.79 (2H,t), 7.62 (1H,t). (Found: C, 77.48; H, 3.89; N, 17.69%. Calc. for $C_{10}H_6N_2$: C,77.90; H,3.92; N,18.17%).

4-(2-Methylquinoline) isocyanide 2d ν (CH_2Cl_2) 2125 cm^{-1}; δ: 8.10 (1H,d), 8.04 (1H,d), 7.77 (1H,t), 7.63 (1H,t), 7.27 (1H,s), 2.66 (3H,s).

4-(N,N-Dimethylaminophenyl) isocyanide 2e ν (CH_2Cl_2) 2110 cm^{-1}; ν: 7.23 (2H,d), 6.57 (2H,d), 2.98 (6H,s).

Typical Procedure for Radical Addition to Isocyanides 2

All the operations were performed under inert atmosphere in well degassed solvents. Until irradiation was started (150W tungsten lamp) the reaction vessel was wrapped with an aluminum foil.

a) Radical Addition to p-Nitrophenyl Isocyanide 2a

p-Nitrophenyl isocyanide 2a (800 mg; 5.40 mmol) was dissolved in dry benzene (15 ml) and a portion of this solution (4 ml) was used to dissolve the thiohydroxamic ester 1h (150 mg; 0.36 mmol). This ester solution was then added over 40 min. via syringe pump, to the remaining irradiated isocyanide solution (11 ml) kept at a constant temperature of 45°C.

The irradiation was continued for 15 min. after the end of addition. Then, the cooled reaction mixture was diluted with ether and stirred for 15 min. at RT. Concentration followed by a chromatography on silica (C_6H_6/Et_2O 96/4 then CH_2Cl_2; under inert atmosphere, in the dark) afforded the pure amide 5h. During the separation most of 2a was recovered (500 mg, 62%) and could be recycled.

The compounds 5i and 5h obtained in this way (Table 4) had identical spectral data with the authentic amide samples prepared from the corresponding acyl chlorides and p-nitroaniline in THF.

N-(p-Nitrophenyl)-2-Phenylpropionamide 5i mp. (Hexane/EtOAc): 119-120°C ν (CH_2Cl_2) 3415, 1708 cm^{-1}; δ (^1H): 8.14 (2H,d), 7.77 (1H,s), 7.62 (2H,d), 7.32-7.17 (5H,m), 3.05 (2H,t), 2.72 (2H,t); δ (^{13}C): 171.1 (s), 143.7 (s), 143.3 (s), 140.1 (s), 128.7 (d), 128.3 (d), 126.6 (d), 125.0 (d), 119.1 (d), 39.4 (t), 31.3 (t); m/z: 270 (5.5%); (Found: C, 66.58; H, 5.10; N, 10.15%. Calc. for $C_{15}H_{14}N_2O_3$ C, 66.65; H, 5.22; N, 10.37%).

N-(p-Nitrophenyl)-arachidonamide 5h ν (CH_2Cl_2) 3421, 1705 cm^{-1}; δ (^1H): 8.25 (1H,s), 8.15 (2H,d), 7.73 (2H,d), 5.32 (8H,m), 2.77 (6H,m), 2.41 (2H,t) 2.13 (2H,m), 2.00 (2H,m), 1.78 (2H,m), 1.26 (6H,m); 0.85 (3H,t); δ (^{13}C): 171.3 (s), 143.6 (s), 143.4 (s), 130.6 (d), 129.2 (d), 128.6 (d), 128.3 (d), 127.9 (d), 127.7 (d), 127.4 (d), 125.1 (d), 119.1 (d), 36.9 (t), 31.5 (t), 29.3 (t), 27.2 (t), 26.5 (t), 25.6 (t), 25.0 (t), 22.5 (t), 14.1 (q); m/z (%): 424 (4%) M+ [Found: m/z, 424.2728, $C_{26}H_{36}N_2O_3$ (M+) requires 424.2726].

b) Radical Addition to 3-Pyridyl isocyanide 2b

To the cooled solution of 2b (5.25 mmol) in CH_2Cl_2 (15 ml) was successively added freshly distilled trifluoroacetic acid (7.5 µl; 0.09 mmol) and the thiohydroxamic ester 1 (0.75 mmol). After irradiation (see Table 4) the solvent was evaporated and the residue warmed under vacuum (30°C; 0.2 mm Hg). At this stage, the pyridyl thioimidates 3 could be hydrolyzed without further purification. Isolation of the thioimidates 3 was feasible after neutralization with NEt_3 (12.5 µl; 0.09 mmol) followed by flash chromatography on silica gel (CH_2Cl_2 then EtOAc).

Thioimidate 3a δ: 8.55 (1H,d), 8.25 (1H,d), 8.10 (1H,s), 7.55 (1H,t), 7.40 (1H,d), 7.28-7.10 (8H,m), 3.04-2.96 (2H,m), 2.91-2.83 (2H,m).

Thioimidate 3b δ: 8.55 (1H,d), 8.25 (1H,d), 8.10 (1H,s), 7.55 (1H,t), 7.40 (1H,d), 7.20-7.10 (3H,m), 2.74 (2H,t), 1.70 (2H,m), 1.24 (24H,s), 0.86 (3H,t).

Thioimidate 3c δ: 8.55 (1H,d), 8.25 (1H,d), 8.10 (1H,s), 7.55 (1H,t), 7.40 (1H,d), 7.20-7.10 (3H,m), 5.32 (2H,m), 2.54 (2H,t), 1.98 (4H,d), 1.65 (2H,m), 1.25 (20H,m) 0.86 (3H,t).

Thioimidate 3d δ: 8.55 (1H,d), 8.25 (1H,d), 8.10 (1H,s), 7.55 (1H,t), 7.40 (1H,d), 7.20-7.10 (3H,m), 5.33 (4H,m), 2.75 (2H,t), 2.54 (2H,t), 2.00 (4H,d), 1.65 (2H,m), 1.28-1.23 (14H,m), 0.87 (3H,m).

Thioimidate 3e δ: 8.55 (1H,d), 8.25 (1H,d), 8.10 (1H,s), 7.55 (1H,t), 7.40 (1H,d), 7.20-7.10 (3H,m), 2.50 (1H,tt), 2.00 (2H,d), 1.81-1.11 (8H,m).

Thioimidate 3f δ: 8.55 (1H,d), 8.25 (1H,d), 8.10 (1H,s), 7.55 (1H,t), 7.40 (1H,d), 7.20-7.10 (3H,m), 2.61 (1H,m), 1.82 (1H,m), 1.50 (1H,m), 1.24 (3H,d), 0.91 (3H,t).

Thioimidate 3g δ: 8.55 (1H,d), 8.25 (1H,d), 8.10 (1H,s), 7.55 (1H,t), 7.40 (1H,d), 7.20-7.10 (3H,m), 1.43 (9H,s).

After being hydrolysed in a dioxane/water (80/20, v/v) solution at RT (see Table 5) the amides 5 obtained had identical spectral data with the authentic amides prepared from the corresponding carboxylic acid and 3-aminopyridine in dry CH_2Cl_2 with dicyclohexylcarbodiimide (DCC) as a coupling agent.

Amide 5a mp. (benzene/$CHCl_3$) 124-125°C, ν (CH_2Cl_2) 3420, 1693 cm^{-1}; δ(^1H): 8.40 (1H,d), 8.28 (1H,d), 8.12 (1H,d), 7.71 (1H,s), 7.31-7.17 (6H,m), 3.04 (2H,t), 2.68 (2H,t); δ(^{13}C): 171.6 (s), 144.6 (d), 140.9 (d), 140.4 (s), 135.5 (s), 128.6 (d), 128.3 (d), 127.7 (d), 126.4 (d), 123.9 (d), 38.9 (t), 31.4 (t); m/z (%): 226 (31) M+, 105 (41), 94 (100), 91 (72); (Found: C, 73.77; H, 6.34; N, 11.78% Calc. for $C_{14}H_{14}N_2O$ C, 74.31; H, 6.23; N, 12.38%).

Amide 5b mp. (benzene) 95-97°C; ν (CH_2Cl_2) 3420, 1691 cm^{-1}; δ: 8.60 (1H,d), 8.30 (1H,d), 8.22 (1H,d), 8.00 (1H,s), 7.20 (1H,dd), 2.39 (2H,t), 1.68 (2H,m), 1.21 (24H,s), 0.85 (3H,t), (Found: C, 75.62; H, 10.82; N, 8.03%. Calc. for $C_{21}H_{36}N_2O$ C, 75,85; H, 10.91; N, 8.42%).

Amide 5c mp (benzene) 30-33°C; ν ($CHCl_3$) 3423, 1696 cm^{-1}; δ: 9.20 (1H,s), 8.50 (1H,d), 8.25 (1H,d), 8.17 (1H,d), 7.20 (1H,dd), 5.28 (2H,m), 1.96 (4H,m), 1.68 (2H,m), 1.33-1.20 (20H,m), 0.84 (3H,t); m/z (%): 358 (77.5%) M+ [Found: m/z, 358.2981, $C_{23}H_{38}N_2O$ (M+) requires 358.2984].

Amide 5d ν ($CHCl_3$) 3424, 1695 cm^{-1}; δ: 8.54 (1H,d) 8.31 (1H,d), 8.20 (1H,d), 7.75 (1H,s), 7.25 (1H,dd), 5.34 (4H,m), 2.75 (2H,t), 2.38 (2H,t), 2.01 (4H,m), 1.71 (2H,m), 1.35-1.25 (14H,m), 0.87 (3H,t); m/z (%): 356 (65.4%) M+ [Found: m\z, 356.2824, $C_{23}H_{36}N_2O$ (M+) required 356.2828].

Amide 5e mp. (Hexane / $CHCl_3$) 134-135°C ν (CH_2Cl_2) 3430, 1696 cm^{-1}; δ: 8.70 (1H,s), 8.55 (1H,d), 8.26 (1H,d), 8.17 (1H,d), 7.22 (1H,dd), 2.29 (1H,tt), 1.94-1.15 (10H,m); [Found: C, 70.83; H, 8.24; N, 13.62%. Calc. for $C_{12}H_{16}N_2O$ C, 70.55; H, 7.90; N, 13.72%].

Amide 5f ν ($CHCl_3$) 3423, 1695 cm^{-1}; δ: 9.20 (1H,s), 8.68 (1H,d), 8.21 (1H,d), 8.10 (1H,d), 7.17 (1H,dd), 2.31 (1H,m), 1.63 (1H,m), 1.40 (1H,m), 1.10 (3H,d), 0.84 (3H,t); m/z (%): 178 (28%) M+ [Found: m/z, 178.1100, $C_{10}H_{14}N_2O$ (M+) requires 178.1106].

Amide 5g mp. (benzene) 123-124°C (lit.[27] 127°C); ν (CH_2Cl_2) 3439, 1682 cm^{-1}; δ: 8.62 (1H,s), 8.49 (1H,d), 8.06 (1H,d), 7.95 (1H,d), 7.02 (1H,dd), 1.13 (9H,s).

The sulfides 4 resulting from the background rearrangement reaction (Table 4), which were not isolated during the purification of the pyridyl thioimidates 3, were easily prepared by irradiation of a solution of the ester 1 (0.20g) in dry CH_2Cl_2 (5 ml) at 0°C and purified by preparative tlc on silica (CH_2Cl_2).

Sulfide 4a ν: (CH_2Cl_2) 1580, 1125 cm^{-1}; δ: 8.45 (1H,d), 7.46 (1H,t), 7.37-7.15 (6H,m), 6.98 (1H,t), 3.41 (2H,t), 3.05 (2H,t).

Sulfide 4c ν (CH_2Cl_2): 1579, 1124 cm^{-1}; δ: 8.45 (1H,d), 7.45 (1H,t), 7.15 (1H,d), 6.94 (1H,t), 5.33 (2H,m), 3.14 (2H,t), 2.00 (4H,m), 1.78 (2H,m), 1.25-1.19 (20H,m), 0.86 (3H,t).

Sulfide 4d ν ($CHCl_3$): 1580, 1126 cm^{-1}; δ: 8.40 (1H,d), 7.43 (1H,t), 7.13 (1H,d), 6.91 (1H,t), 5.34 (4H,m), 3.14 (2H,t), 2.75 (2H,t), 2.01 (4H,m), 1.67 (2H,m), 1.42-1.28 (14H,m), 0.87 (3H,t).

Sulfide 4e ν (CH_2Cl_2): 1580, 1125 cm^{-1}; δ: 8.38 (1H,d), 7.40 (1H,t), 7.11 (1H,d), 6.90 (1H,t), 3.76 (1H,m), 2.02 (2H,m), 2.79-1.20 (8H,m).

Sulfide 4f ν (CH_2Cl_2): 1577, 1125 cm^{-1}; δ: 8.41 (1H,d), 7.45 (1H,t), 7.15 (1H,d), 7.00 (1H,t), 3.90 (1H,m), 2.35 (1H,m), 1.68 (1H,m), 1.36 (3H,d), 1.05 (3H,t).

Sulfide 4h ν (CH_2Cl_2): 1579, 1126 cm^{-1}; δ: 8.43 (1H,d), 7.45 (1H,t), 7.17 (1H,d), 6.94 (1H,t), 5.36 (8H,m), 3.16 (2H,t), 2.81 (6H,m), 2.23 (2H,m), 2.03 (2H,m), 1.78 (2H,m), 1.30-1.24 (6H,m); 0.88 (3H,t).

Regeneration of the Starting Carboxylic Acids 6

All these experiments were performed under inert atmosphere with rigorous exclusion of moisture. Solvents and reagents were dried before using by conventional methods.

Hydrolysis of N-(3-Pyridyl)-amides 5a-5f

a) Cleavage by CS_2 procedure: To a THF solution (1.0 ml) of hexamethyldisilazane (0.17 ml, 0.81 mmol) cooled at -20°C, a solution of n-BuLi (0.74 mmol) in hexane (1.6N) was added dropwise. After stirring for 30 min., the amide (0.74 mmol) in THF (2ml) was added at -20°C and the temperature allowed to rise to room temperature. To this solution, CS_2 (0.13 ml, 2.21 mmol) in THF (0.5 ml) was added dropwise and stirring was continued overnight.

To obtain the thiol-acid from amide 5a, the reaction mixture was poured into a chilled aqueous NaOH (10%) solution and washed with ether. The aqueous layer was acidified by H_2SO_4(25%; v/v) and extracted with benzene. Evaporation of solvent furnished the pure product in 80% yield, which dimerized on standing.

$Ph(CH_2)_2COSH$, δ: 7.35-7.13 (5H,m), 2.95 (4H,s).

$[Ph(CH_2)_2COS]_2$, ν (CH_2Cl_2) 1720, 1610, 1135 cm^{-1}; δ(^1H): 7.35-7.13 (10H,m), 3.05 (8H,s); δ(^{13}C): 192.7 (s), 139.4 (s), 128.7 (d), 128.3 (d), 126.6 (d), 44.3 (t), 31.2 (t); m/z (%): 133 (68), 105 (100), 91 (88).

For regeneration of the carboxylic acid, the reaction mixture was diluted with THF (1 ml) and treated with $PhSeO_2H$ (138 mg, 0.73 mmol). After stirring at RT for 5 hrs., the resulting mixture was poured into chilled aqueous NaOH and washed with ether. The acidified (25% H_2SO_4, v/v) aqueous layer was extracted with ether. The combined organic extracts gave pure acid 6 upon removal of solvent in moderate to good yield (see Table 5).
b) Cleavage via Imidoyl chloride 8: The reaction conditions were identical to those described for N-(p-nitrophenyl)-amides. It is to be noted that structurally related compound 3a did not react with an excess of i-BuOH at 60°C.

Hydrolysis of N-(p-Nitrophenyl)-amides 5h-5i

Method A: A solution of amide (1.15 mmol) in CH_2Cl_2 (2 ml) was quickly added to a suspension of PCl_5 (249 mg, 1.2 mmol) in CH_2Cl_2 (1 ml) at 0°C.

Method B: Phosgene (118 mg, 1.20 mmol) as a solution in CH_2Cl_2 (2 ml) was added dropwise to a solution of the amide (1.15 mmol) in CH_2Cl_2 (2 ml) at 0°C.

To the above solutions (15 min. after PCl_5 dissolution or at the end of phosgene addition) dry pyridine (97 µl; 1.2 mmol) in CH_2Cl_2 was slowly added and the reaction mixture was stirred at room temperature for 30 min. The resulting solution was treated with dry i-BuOH (0.6 ml; 6.5 mmol). After the formation of a precipitate, the mixture was stirred for 3 additional hours and then poured into cold water. Extraction with CH_2Cl_2, washing with 5% aqueous HCl (v/v) and with H_2O followed by evaporation of CH_2Cl_2 furnished the ester 9, which could be used in the next step without further purification.
iso-Butyl ester 9a ν (CH_2Cl_2) 1726 cm^{-1}; δ: 7.18 (5H,m), 3.82 (2H,d), 2.92 (2H,t), 2.60 (2H,t), 1.87 (1H,m), 0.89 (6H,d).

This compound, 9a, had identical spectral data as the authentic ester sample prepared from dihydrocinnamic acid (10 mmole) and iso-butanol (11 mmol) in CH_2Cl_2 (5 ml) using DCC (11 mmol) and catalytic amount of (1.1 mmol) 4-dimethylaminopyridine. The yield was 95%.

iso-Butyl ester 9b ν (CH_2Cl_2) 1725 cm^{-1}; δ: 3.82 (2H,d), 2.29 (2H,t), 1.90 (1H,m), 1.59 (2H,m), 1.23 (24H,s), 0.90 (6H,m), 0.84 (3H,t).

iso-Butyl ester 9c ν (CH_2Cl_2) 1726 cm^{-1}; δ: 5.32 (8H,m), 3.82 (2H,d), 2.77 (6H,m), 2.30 (2H,t), 2.14-1.95 (4H,m), 1.86 (1H,m), 1.26 (6H,m), 0.92-0.87 (9H,m).

Hydrolysis of iso-Butyl Esters 9

A solution of ester 9 (0.55 mmol) in ethanol (25 ml) containing 3N aqueous NaOH (5 ml) was stirred for 12 hrs. at room temperature. The reaction mixture was then carefully neutralized by H_2SO_4, filtered and the precipitate (Na_2SO_4) washed with ethanol. The solvents were evaporated under vacuum then residual water and i-BuOH were removed by azeotropic distillation with benzene. A filtration through a silica column, when necessary, furnished the carboxylic acid 6 in pure form (n.m.r.) (see Table 6).

Quantification of CO_2 Liberated During the Reaction Between Ester 1a and Isocyanide 2a

A constant flow of argon was maintained during the photolysis of the reaction mixture. The gaseous mixture was bubbled into distilled and degassed H_2O (3 ml) containing $Ba(OH)_2$. $8H_2O$ (500 mg; 1.58 mmol). After the decomposition of ester 1a was complete, the precipitated $BaCO_3$ was filtered under inert atmosphere and dried (250°C) to a constant weight (0.143 g, 97%).

Photolysis of Ester 1h in the Presence of ^{13}C-Enriched Isocyanide 2a

An experiment using ester 1h and isocyanide 2a labelled on the isocyanide function (^{13}C, 7.5% enriched) furnished after purification, the amide 5h labelled on the amide function as determined by comparative ^{13}C-n.m.r. measurements (^{13}C, 7.2% enriched). This demonstrated that the amide was exclusively formed from radical addition to the isocyanide.

Preparation of the Phenylselenide Derived from Arachidonic Acid.

The thiohydroxamic ester of arachidonic acid 1h (54 mg; 0.131 mmol) was dissolved in benzene (4 ml) and diphenyl diselenide (81 mg; 0.26 mmol) was added. The resulting solution was irradiated (150W tungsten lamp) at 45°C for 30 min. The reaction mixture was concentrated under vacuum and the pure product was isolated by prep. t.l.c. on silica (2 successive elutions: hexane then hexane/CH_2Cl_2/Et_2O, 10/9/1. The phenylselenide derivative obtained (39.1 mg, 72%) was a pale yellow oil. ν ($CHCl_3$) 1576, 1475 and 1437 cm^{-1}; δ (^1H): 7.52-7.46 (2H,m), 7.26-7.22 (3H,m), 5.40-5.35 (8H,m), 2.91 (2H,t), 2.81 (6H,m), 2.18 (2H,m), 2.03 (2H,m), 1.76 (2H,m), 1.29 (6H,m), 0.88 (3H,t). δ (^{13}C): 141.9 (s), 132.5 (d), 130.5 (d), 129.0 (d), 128.8 (d), 128.6 (d), 128.2 (d), 127.9 (d), 127.5 (d), 126,7 (d), 31.5 (t), 29.9 (t), 29.3 (t), 27.3 (t), 27.2 (t), 25.6 (t), 22.6 (t), 14.1 (q); M/z (%): 417 (12) M+1, 416 (43) M+, 339 (15.3), 158 (50.3), 79 (100) [Found:M/z, 416.1972, $C_{25}H_{36}{}^{80}Se$ (M+) requires 416.1982].

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