

New reactions for use in natural products chemistry

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in collaboration with

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I. STEREOSPECIFICITY IN RADICAL REACTIONS

Abstract - Radicals, generated from isopropylidene uronic esters of N-hydroxy-2-thiopyridone, add readily to electron-poor alkenes in a stereospecific fashion, leading to functionalised chain-elongated furanosides and *D*-ribo-nucleosides through carbon-4 (Table 1). The directive effect of the ketal group in controlling the newly created chirality is noteworthy.

As is well appreciated an asymmetric carbon atom immediately loses its asymmetry when it becomes a non-caged carbon radical.¹ Synthesis starting with the chiral pool² and using radical chain chemistry, can only be stereospecific if one or more asymmetric centres control the formation of the newly created chirality.³

Our recent work on the radical chemistry of tartaric acid monomethyl ester dimethyl ketal **1** has shown that carbon-carbon bond formation from the derived radical **2** has remarkable stereoselectivity (retention with 92% e,e).

Now many important natural products are (formally) derived by chain elongation at position 5 of pentoses, or at position 6 of hexoses.⁵ It occurred to us that the carboxyl derived radical chemistry that we have recently⁶ introduced would permit stereospecific reactions of radicals derived from uronic acids suitably protected by strategically placed ketal functions. The results are summarised in Table (1).

The diacetone ketal of glucuronic acid **3** on conversion to its N-hydroxy-2-thiopyridone derivative **4** and irradiation with tungsten light in the usual way⁶ in presence of methyl acrylate **5** gave the expected derivative **6** as a mixture of diastereoisomers. Oxidation to sulphoxide and elimination afforded the unsaturated ester **7** as a single compound. Oxidation with ruthenium tetra-oxide⁴ gave back pure starting material **3**. A similar series of reactions was carried out using phenylvinyl sulphone **8** as a radical trap. This afforded the mixed isomers **9** and after elimination the pure olefin **10**. A small amount of the double addition adduct **11** (3%) was also seen in the methyl acrylate experiments, but not with the phenylvinyl sulfone as this is not subject to radical polymerisation.

Similarly, the ribofuranuronic acid derivative⁷ **12** (using phenylvinylsulphone) was converted to a mixture of stereoisomers **13** which on oxidation and elimination gave a single compound **14** ($[\alpha]_D + 2.4^\circ$ CHCl₃). The structure was assigned from analysis of its 200 MHz spectrum.

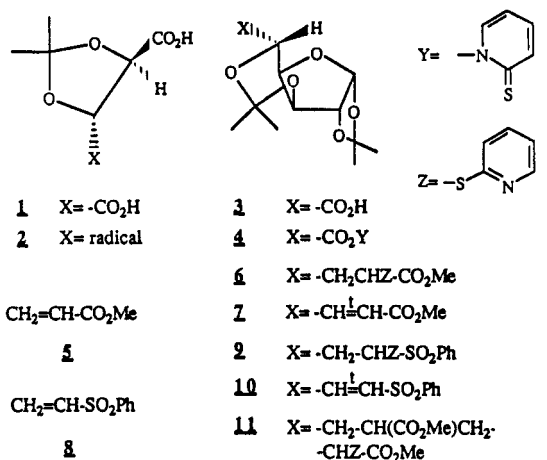


TABLE 1

Uronic Acid	Olefin (eq.)	Addition Product (%)	Elimination Product (%)	Retention (R) or Inversion (I)
3	5 (4)	6 (57), 11 (3)	7 (72)	R
3	8 (5)	9 (68)	10 (85)	R
12	8 (5)	13 (95)	14 (62)	R
15	8 (5)	16 (95)	17 (50)	I
18	8 (5)	19 (95)	20 (60)	R
21	8 (5)	22 (60)	23 (60)	R

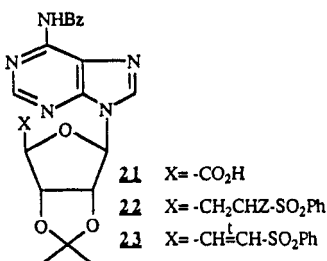
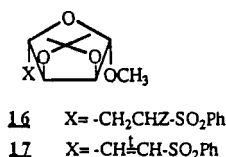
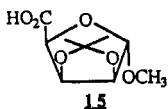
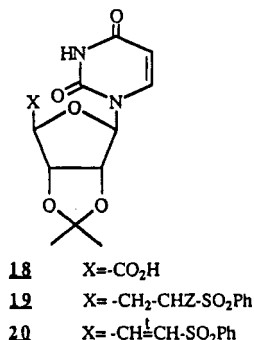
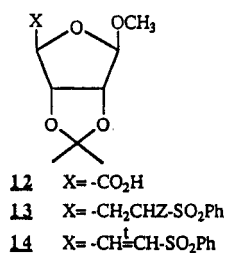


TABLE 2

Uronic Acid	$[M_D]^{22}$ (Solvent)	$\Delta [M_D]^{22}$ Values
<u>12</u>	-146 (CHCl ₃)	
<u>14</u>	+8.2 (CHCl ₃)	<u>14-12</u> = +154
<u>15</u>	+43.4 (CHCl ₃)	
<u>17</u>	-8.1 (CHCl ₃)	<u>17-15</u> = -51.5
<u>18</u>	-143 (DMF)	
<u>20</u>	+206 (DMF)	<u>20-18</u> = +349
<u>21</u>	-260 (DMF)	
<u>23</u>	+227 (DMF)	<u>23-21</u> = +487

In contrast the D-lyxofuranuronic acid derivative **15** gave, on addition of the radical to phenylvinylsulfone, the adducts **16** which on oxidation and elimination afforded a single unsaturated adduct **17** ($[\alpha]_D - 2.4^\circ$ in CHCl₃) in which the side chain was completely inverted as judged by analysis of its n.m.r. spectrum.

The uridine derivative⁸ **18** was a particularly important case. The derived radical gave a good yield of adduct **19** with phenylvinylsulfone which on oxidation and elimination afforded the vinyl sulfone **20**, m.p. 111-114°, $[\alpha]_D +49.20^\circ$ (DMF), as a single compound. Its ¹H and ¹³C NMR spectra were entirely compatible with the structure assigned.

Finally, the adenine derivative **21** afforded with phenylvinyl sulfone an adduct **22** which on oxidation and elimination gave the adduct **23**, m.p. 115-118°, $[\alpha]_D +41.6^\circ$ (DMF). The configuration of **23** was ascertained by n.m.r. spectroscopy.

An analysis (Table 2) of the (M)_D values of the compounds described in this article is in agreement with the retention of configuration in all the compounds studied except for the transformation **15** → **17** where inversion is seen. The directing effect of the ketal function on the chirality obtained is remarkable.

These results show the dominant effect of steric bulk⁴ of the ketal group in controlling the chirality of the derived radical adduct. This stereochemical specificity will permit extensive manipulation of the functionalised ribose side chain in naturally occurring D-ribo-nucleosides at carbon-4', an objective of current relevance.

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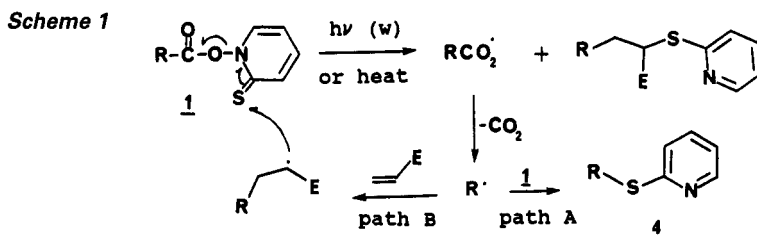
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II. ROLE OF ORGANIC TELLURIDES AS ACCUMULATORS AND EXCHANGERS OF CARBON RADICALS

Abstract. Primary carbon radicals, generated by photolysis of acyl derivatives of *N*-hydroxy-2-thiopyridone, exchange efficiently on diisopropyl telluride to give isopropyl radicals which can in turn be trapped by radicophilic olefins.

The use of radical reactions in Organic Synthesis is becoming common place.¹ The reason for this is that systems are now available for the generation of disciplined radicals, which give high yields of single products.² Carbon radical reactions can also be made stereospecific if there is appropriate functionality near to the radical center.³

In the last five years we have shown that the acyl derivatives of thiohydroxamic acids are an excellent source of disciplined radicals.² Scheme 1 summarizes a typical reaction using derivatives **1** of the readily available and inexpensive⁴ *N*-hydroxy-2-thiopyridone. When the olefin ($\text{CH}_2=\text{CHE}$) is not very radicophilic, path A is seen giving the thiopyridines **4**, whereas if the E function in the olefin is strongly electron withdrawing, then addition occurs smoothly by path B⁵.

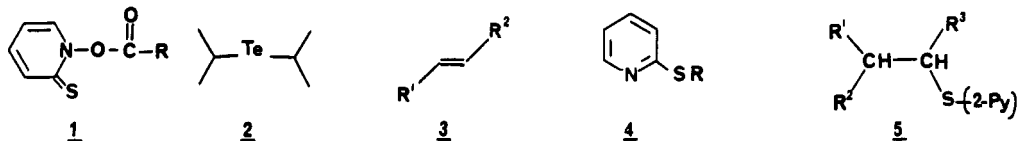


The idea of a radical accumulator has been discussed before⁴, but without experimental success. Recently, Zard⁶ has reexamined the mechanism of the acyl xanthate photolysis reaction that we invented some time ago.⁷ The original interpretation has been ingeniously modified by recognition that the acyl radicals produced are degenerate and exchange continuously with the original acyl xanthate. Thus, an accumulation of radicals is ensured.

In this article we described a different radical accumulator which serves also as a radical exchanger. Thus, a radical R^{\bullet} derived from **1** could be conceived to add to a compound of type MR'_n to give a radical $\text{R-MR}'_n$. If $\text{R}=\text{R}'$, then the new radical would be degenerate and act as a radical accumulator. If, on the other hand $\text{R}\neq\text{R}'$, and if the $\text{R}'\text{-M}$ bond was weaker than the newly formed R-M bond, then the adduct radical would fragment into a new radical R'^{\bullet} and $\text{R-MR}'_{n-1}$. Thus there would be radical exchange.

It seemed to us that dialkyltellurides⁸ would be suitable for this role. Thus, photolysis of acyl derivative **1a** in the presence of diisopropyl telluride **2** (1 equiv.) gave a smooth exchange reaction to furnish methyl isopropyl telluride and the isopropyl radical. The sulfides **4a** and **4b** at once disclosed the efficiency of **2** in capturing methyl radicals.

With this result we were in a position to study the interception of isopropyl radicals formed from **2**, with various electron deficient olefins. As shown in Table 1, irradiation of esters **1** in presence of **2** resulted in addition of the isopropyl radical to various olefins in moderate to good yields. In some cases, however, small amounts (<20%) of the adducts of primary radicals with olefins were also detected. As expected, increasing the quantity of diisopropyl telluride **2** favoured the addition of isopropyl radical. Of course, complete inertness of **2** toward the olefin **3a** was established in a control experiment.



a, $\text{R}=\text{CH}_3$

b, $\text{R}=(\text{CH}_3)_2\text{CH}$

c, $\text{R}=\text{CH}_3(\text{CH}_2)_{14}$

d, $\text{R}=\text{PhCH}_2\text{CH}_2$

a, $\text{R}^1=\text{H}$, $\text{R}^2=\text{SO}_2\text{Ph}$

b, $\text{R}^1=\text{H}$, $\text{R}^2=\text{CO}_2\text{CH}_3$

c, $\text{R}^1=\text{CH}_3$, $\text{R}^2=\text{CN}$

d, $\text{R}^1=\text{CH}_3$, $\text{R}^2=\text{CO}_2\text{CH}_3$

a, $\text{R}=\text{CH}_3$

b, $\text{R}=(\text{CH}_3)_2\text{CH}$

c, $\text{R}=\text{CH}_3(\text{CH}_2)_{14}$

d, $\text{R}=\text{PhCH}_2\text{CH}_2$

a, $\text{R}^1=\text{H}$, $\text{R}^2=(\text{CH}_3)_2\text{CH}$, $\text{R}^3=\text{SO}_2\text{Ph}$

b, $\text{R}^1=\text{H}$, $\text{R}^2=(\text{CH}_3)_2\text{CH}$, $\text{R}^3=\text{CO}_2\text{CH}_3$

c, $\text{R}^1=\text{H}$, $\text{R}^2=\text{CH}_3(\text{CH}_2)_{14}$, $\text{R}^3=\text{SO}_2\text{Ph}$

d, $\text{R}^1=\text{H}$, $\text{R}^2=\text{PhCH}_2\text{CH}_2$, $\text{R}^3=\text{SO}_2\text{Ph}$

e, $\text{R}^1=\text{CH}_3$, $\text{R}^2=(\text{CH}_3)_2\text{CH}$, $\text{R}^3=\text{CO}_2\text{CH}_3$

f, $\text{R}^1=\text{CH}_3$, $\text{R}^2=(\text{CH}_3)_2\text{CH}$, $\text{R}^3=\text{CN}$

TABLE 1^a

Entry	Ester 1 (mmol)	Diisopropyl Telluride	Alkene 3 (mmol)	Products ^b (% yield)
1	<u>1a</u> (0.07)	(0.07)	<u>3a</u> (0.14)	<u>5a</u> (61)
2	<u>1a</u> (0.08)	(0.16)	<u>3a</u> (0.16)	<u>5a</u> (66)
3	<u>1b</u> (0.14)	(0.14)	<u>3a</u> (0.14)	<u>5a</u> (66), <u>4b</u> (13)
4	<u>1b</u> (0.16)	(0.16)	<u>3b</u> (0.16)	<u>5b</u> (65), <u>4b</u> (16)
5	<u>1b</u> (0.13)	(0.13)	<u>3c</u> (0.13)	<u>5f</u> (28), <u>4b</u> (43)
6	<u>1c</u> (0.08)	(0.08)	<u>3a</u> (0.16)	<u>5a</u> (64), <u>5c</u> (20)
7	<u>1c</u> (0.07)	(0.14)	<u>3a</u> (0.14)	<u>5a</u> (68), <u>5c</u> (28)
8	<u>1d</u> (0.08)	(0.16)	<u>3a</u> (0.16)	<u>5a</u> (50), <u>5d</u> (20)
9	<u>1d</u> (0.09)	(0.45)	<u>3a</u> (0.18)	<u>5a</u> (72)

TABLE 2^a

Entry	Ester 1 (mmol)	Alkene 3 (mmol)	Products ^b (% yield)
1	<u>1b</u> (0.15)	<u>3a</u> (0.30)	<u>5a</u> (85)
2	<u>1b</u> (0.1)	<u>3a</u> (0.1)	<u>5a</u> (75)
3	<u>1b</u> (0.2)	<u>3b</u> (0.2)	<u>5b</u> (65), <u>4b</u> (16)
4	<u>1b</u> (0.12)	<u>3c</u> (0.12)	<u>5f</u> (22), <u>4b</u> (49)
5	<u>1b</u> (0.1)	<u>3c</u> (0.5)	<u>5f</u> (43), <u>4b</u> (21)
6	<u>1b</u> (0.1)	<u>3c</u> (1.0)	<u>5f</u> (60), <u>4b</u> (12)
7	<u>1b</u> (0.1)	<u>3d</u> (0.5)	<u>5a</u> (30), <u>4b</u> (32)
8	<u>1b</u> (0.1)	<u>3d</u> (1.0)	<u>5a</u> (50), <u>4b</u> (18)
9	<u>1c</u> (0.1)	<u>3a</u> (0.2)	<u>5c</u> (90)
10	<u>1d</u> (0.1)	<u>3a</u> (0.2)	<u>5d</u> (70), <u>4d</u> (25)
11	<u>1d</u> (0.1)	<u>3a</u> (0.5)	<u>5d</u> (82), <u>4d</u> (15)

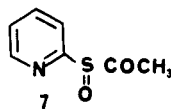
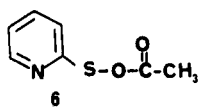
a) Reactants in CDCl₃ are photolyzed (tungsten lamp, 150W) at room temperature. b) Yields are determined by N.M.R.

When the isobutyric acid derivative 1b was used, the intermediate radical [•]Te(CHMe₂)₃ was of course degenerate and thus acted as a radical accumulator. There was no obvious favourable effect on the addition to the radicophilic olefin.

The results given in Table 1 demonstrated that the initially foreseen expulsion of isopropyl radical from 2 and its capture by an olefin was a feasible process. Moreover, it appeared to be reasonably efficient without demanding excess of the tellurium compound 2. However, the radical accumulating function of diisopropyl telluride 2 had to be justified before extending this concept to the generation of other radicals (tertiary, benzyl, allyl, etc.). Thus, a series of experiments was run to determine the extent of radical addition to the olefins 3 in the absence of diisopropyl telluride 2 (Table 2). A comparison between entries 3-5 of Table 1 and entries 2-4 of Table 2 leads to the conclusion that there is no enhancement of yield in addition reactions using the telluride 2 as accumulator of radicals.

We have, therefore, demonstrated an efficient exchange of primary radicals into secondary radicals, but we have not shown that this process has meaningful use in synthetic chemistry. Indeed, the iodide exchange reactions of Minisci⁹ are of more practical importance.

In the course of this work, the photolysis of the acetate 1a was studied at various temperatures. Irradiation of 1a (N.M.R. methyl signal at 2.39 ppm, I.R. at 1811 cm⁻¹) at -40° in CDCl₃ gave three methyl signals at 2.08, 2.59 and 2.23 ppm. in the N.M.R. spectrum. The first two were due to acetic acid and methyl pyridyl sulfide 4a, respectively. The infra-red spectrum displayed a new carbonyl absorption at 1824 cm⁻¹. Attempts to isolate this product were unsuccessful due to its instability. Addition of aniline to the photolysis mixture, however, resulted in quantitative conversion of the product to acetanilide, which was isolated and characterized. The chemical evidence along with the spectral data showed that the major product of photolysis of 1a at -40° was the rearrangement product 6 (or 7)¹⁰. Photolysis at higher temperatures favoured the formation of methyl pyridyl sulfide 4a with concomitant decrease in the quantity of 6 (or 7).



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III. A NEW AND EFFICIENT REACTION FOR THE SYNTHESIS OF THE CARBON-CARBON BOND

Abstract - Palladium (0) converts tellurides of type $R^1\text{-Te-}R^2$ into coupled product $R^1\text{-}R^2$ and metallic tellurium (as a mirror) in high yield under mild conditions. There is little or no sign of β -elimination and no evidence for cross coupling.

We recently reported that palladium (0) converts aryl derivatives of Bi(III) and Bi(V) to diaryl compounds and metallic bismuth in high yield under mild conditions.¹ More interesting was the fact that tris- β -phenyl-ethylbismuth **1** afforded the coupled product **2** (74%) at room temperature. This coupling was unexpected as Pd(II) species such as **3** are supposed to β -eliminate and not give ligand coupling.² The product of the reaction should have been styrene.³

We decided to examine the effect of Pd(0) on symmetrical and unsymmetrical tellurides.⁴ Bergman⁵ noted that diaryl tellurides treated with degassed Raney nickel gave diaryls in good yield. Uemura and his colleagues⁶ studied the arylation of olefins using Te(IV) compounds and Pd(II). Diaryls were formed in moderate yield in the absence of the olefin. Finally, Uemura⁷ has also examined the carbonylation of aryl- and vinyl-tellurium compounds under the influence of Pd(II) species; Te(O) and Pd(0) are also formed. We have not found any record of a potentially β -eliminatable alkyl residue (with transfer from tellurium) being used in Pd(0) coupling.

Nevertheless a series of tellurides, including four with alkyl residues, have been smoothly coupled (Table) using Pd(0) generated from Pd(OAc)₂ and triethylamine. In only one case was there some indication of β -elimination; there was no scrambling of ligands.

Whilst **4** gave dianisyl **6** in quantitative yield, the ditelluride was much less reactive. Only in HMPA was a good yield obtained. The telluride **7** gave the same coupled product **2** (85%) as had been obtained before from the bismuth derivative **1**. There was some β -elimination to give styrene.

The telluride **8** gave the coupled product **9** (81%). The telluride **10** contained a weak π -adamantyl ligand as well as a stronger phenyl-tellurium bond. Again the yield was good (89%) and g.c. analysis of the total product showed no sign of dianisyl, the likely product of scrambling. The mass spectrum of the total reaction mixture did not show any scrambled product either. Finally telluride **12** gave the coupled product **13** without β -elimination.

The tellurides used in this work were prepared by standard methods.⁴ The two tellurides **10** and **12** were obtained using the photochemical method already reported.⁸ This works well with diaryl ditellurides, but is less efficient with dialkyl ditellurides.

(PhCH₂CH₂)₃Bi (PhCH₂CH₂)₂ (PhCH₂CH₂)₂Pd

TABLE^a

	<u>1</u>	<u>2</u>	<u>3</u>	Entry	Substrate	Solvent	Reaction Time	Product ^b	Yield %
An ₂ Te	(AnTe) ₂	AnAn	(PhCH ₂ CH ₂) ₂ Te	1	<u>4</u>	CH ₃ CN	8h	<u>6</u>	100
<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	2	<u>5</u>	HMPA	7h ^c	<u>6</u>	82
				3	<u>7</u>	CH ₃ CN	10h	<u>2</u>	85 ^d
PhCH ₂ CH ₂ TeCH ₂ Ph	Ph(CH ₂) ₃ Ph	An-Te-t-Ad		4	<u>8</u>	CH ₃ CN	5h	<u>9</u>	81
<u>8</u>	<u>9</u>	<u>10</u>		5	<u>10</u>	CH ₃ CN	7h	<u>11</u>	89
				6	<u>12</u>	CH ₃ CN	7h	<u>13</u>	76
An-t-Ad	An-Te-C ₁₅ H ₃₁	An-C ₁₅ H ₃₁							
<u>11</u>	<u>12</u>	<u>13</u>							

a) All reactions performed with Pd(O) catalyst, prepared *in situ* from Pd(OAc)₂ (1 mmole) and NEt₃ (2 mmole), and the telluride (1 mmole) at 65° under argon atmosphere.

b) All compounds were characterised by m.p. (where appropriate), N.M.R. and Mass Spectrometry.

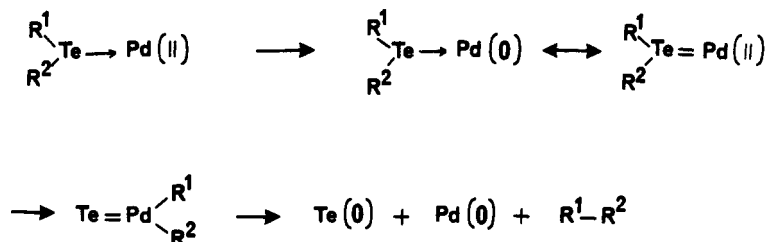
c) An additional equivalent of Pd(O) catalyst was added 3 hrs. after the commencement of the reaction.

d) Some styrene was also formed.

It is relevant to our present findings that recent work⁹ has shown that pyrolysis of (2,2'-bipyridine) diethylpalladium(II) without additive gave, as expected, ethane and ethylene. However, addition of certain olefins like methyl acrylate afforded n-butane with no β -elimination. It is clear that palladium-tellurium bonding of some kind is responsible for the success of our coupling reactions.

Although it would be premature to give an exact mechanism for our new reaction, Scheme 1 outlines a suitable working hypothesis. The other ligands involved remain to be determined.

Scheme 1



This coupling reaction should be useful in the chemistry of Natural Products.

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