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# Preparation of Six Membered Carbocycles by Aryl-Tellurium Mediated Free-Radical Cyclisation

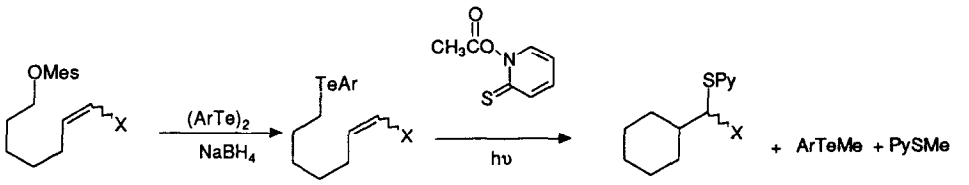
Derek H.R. Barton[a]*, Peter I. Dalko[a,b], Stephan D. Géro[b]

[a]Department of Chemistry, Texas A&M University, College Station,Texas, 77843, USA
[b]Institut de Chimie des Substances Naturelles, CNRS, 91198, Gif-sur-Yvette, France

*Radical cyclisation of various telluro-compounds was examined. Olefins conjugated to an electron withdrawing group, (7, 8, 9, 10, and 11) gave high yields of the corresponding six membered products. Non-activated olefin 23 gave the corresponding thiopyridyl derivative 24 as the only product. The photolysis, using oxime 18 as radicophile for the cyclisation, proceeded slowly at room temperature, and gave only a low yield of products 19 and 20.*

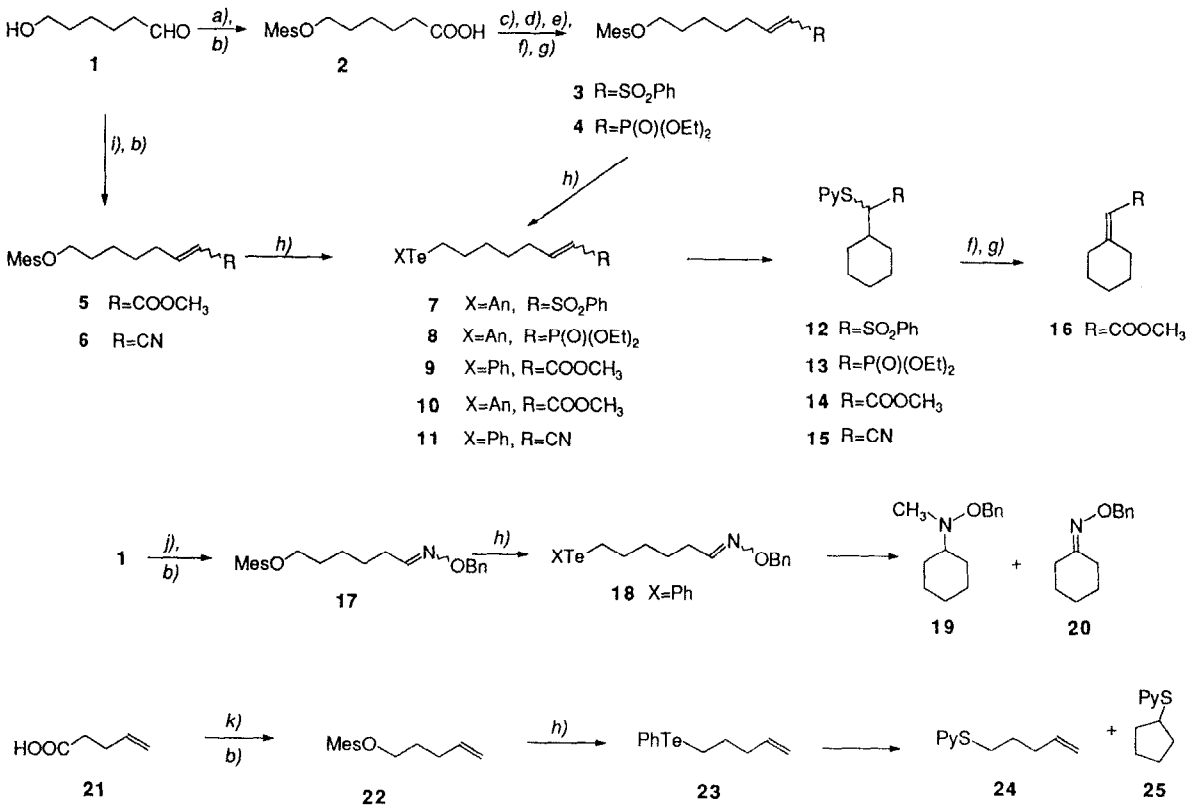
In the last decade, there has been much interest in the preparation of carbocyclic systems by radical chemistry. We recently developed a novel and mild methodology[1] to create carbon centered radicals, which is based on the weakness of the carbon-tellurium bond[2].

This methodology is particularly suitable to generate free-radicals from hydroxylated compounds: the hydroxyl group, converted into a leaving group, can be displaced by the exceptionally nucleophilic aryl-telluride anion (Scheme 1). The so prepared organo-telluride derivatives react with the methyl radical, prepared from the acetyl derivative of *N*-hydroxy-2-thiopyridone[1,3] by irradiation with a tungsten or iodide halogen lamp, to form a relatively strong methyl-tellurium bond with displacement of the alkyl radical. Although our primary intention has been focused on the synthetic application of the reaction, radical cyclofunctionalisation using aryl-tellurium species had not been studied[4]. In this paper we wish to report on the scope and perspectives for this cyclisation.




Scheme 1

In this communication we examine whether the radicals produced might undergo an intramolecular cyclisation reaction either with electrophilic or electron rich systems *versus* the thiocarbonyl of the thiopyridyl moiety. The unsaturated intermediates, required for these studies, **7-11**, were prepared from 6-hydroxy hexanal, **1**. This was readily converted *via* the carboxylic acid **2** to the sulphonate **3** and phosphonate **4** by free-radical decarboxylative alkylation followed by oxidation-elimination of the thiopyridyl group. The ester **5** and nitrile **6** were simply obtained from **1**, by a Wittig reaction, followed by mesylation of the free hydroxyl function. The mesyloxy group was displaced by NaTePh[5] and/or NaTeAn[6], generated *in situ* from the dimer, diaryl-ditellurides[7,8], by $NaBH_4$ reduction[9]. According to the literature data[10], α,β-unsaturated esters are sensitive to 1,4-conjugate addition of tellurium nucleophiles. However, under the conditions applied, we obtained only the desired intermediates. Compounds **7-11** were obtained after purification on short columne of silicagel as pale yelow oiles[11].




*a)* $Na_3IO_4$, $RuO_2$, $CCl_4$, $CH_3CN$, $H_2O$, 2 hours; *b)* MesCl, $Et_3N$, $CH_2Cl_2$; *c)* $(COCl)_2$, $CH_2Cl_2$, DMF cat.; *d)* NaO(SPy); *e)* $CH_2$=CH-R, h $\upsilon$, $CH_2Cl_2$; *f)* MCPBA, $CH_2Cl_2$; *g)* toluene, 110°C, 3 hours; *h)* $(PhTe)_2$ or $(AnTe)_2$, $NaBH_4$, EtOH; *i)* $Ph_3P$=CH-R, toluene, 110°C, overnight; *j)* $NH_2OBn$; *k)* $BH_3$·THF, -78°C, 2 hours.

Scheme 2

| Entry | Transformation | Aryl-telluride | Isolated yield (%) |
|---|---|---|---|
| 1 | **3→7** | $(AnTe)_2$ | 79 |
| 2 | **4→8** | " | 81 |
| 3 | **5→9** | $(PhTe)_2$ | 77 |
| 4 | **6→10** | $(AnTe)_2$ | 77 |
| 5 | **6→11** | $(PhTe)_2$ | 78 |
| 6 | **17→18** | " | 89 |
| 7 | **22→23** | " | 68 |

Table 1

Table 1 summarizes the results of the substitution using different aryl-telluride nucleophiles. The so prepared organo-tellurides were stable under the experimental conditions, under argon. Some decomposition was observed however when the samples were exposed to air and daylight at room temperature over several days.

A typical procedure for the preparation of the organo-tellurides is as follows:
A solution of 50 mg (0.122 mMol) of dianisyl-ditelluride in 0.5 ml of benzene was slowly added to a stirred suspension of 18.5 mg (0.488 mMol) sodium borohydride in 1 ml of ethanol at room temperature, under argon. A vigorous evolution of hydrogen and the disappearance of the dark color was observed. After the mixture was stirred for 10 minutes, a solution of 0.22 mMol of the mesyl compound in 0.5 ml of ethanol was added over a period of one minute. The resulting mixture was stirred for an additional 3 hours at room temperature. The reaction mixture was then diluted with 5 ml of diethyl ether and filtered on a pad of Celite and evaporated *in vacuo*. A small amount of heptane was added and the solution was chromatographed on a short column of silica gel. (The corresponding phenyl derivatives were prepared in the same way.)

Compounds **7**, **8** and **10** underwent radical cyclisation in the presence of *N*-acetoxy-2-thiopyridone and irradiation, according to the procedure described below. In the cases examined, the reaction gave after 15 min. of irradiation at room temperature a clean mixture of the cyclised product, the methyl-anisyl-telluride, and the methyl-thiopyridyl derivative which were separated by short column chromatography. This cyclisation is particularly mild and highly selective, and compatible with a wide range of functional groups. The structure of the cyclised product **14** was confirmed by transforming it into the exocyclic olefin compound **16**, using an oxidation-elimination procedure. The structures of the other cyclic products[11] were deduced from NMR and compared with that of related compound **14**. We summarize in Table 2 some representative examples of the cyclisation.

| Entry | Transformation | Added *N*-acetoxy-2-thiopyridone (eq.) | Isolated yield (%) |
|---|---|---|---|
| 1 | **7→12** | 3.5 | 77 |
| 2 | **8→13** | 3.5 | 53 |
| 3 | **9→14** | 4.0 | 70 |
| 4 | **10→14** | 3.5 | 74 |
| 5 | **11→15** | 4.0 | 69 |
| 6 | **18→19 + 20** | 7.0 | 7(**19**), 8(**20**) |
| 7 | **23→25** | 3.5 | 0 |

Table 2

As Table 2 indicates, the radical cyclisation using phenyl-tellurides was also examined. Entries 3 and 4 show a comparison between the reactions of anisyl-alkyl and phenyl-alkyl tellurides. The intermediate with a phenyl-telluride group also underwent a radical reaction in presence of *N*-acetoxy-2-thiopyridone and irradiation to give the cyclised product in 71% yield. Entry 5 also illustrates that phenyl telluride is a valuable radical precursor. The relatively low yield in entry 2 is probably due to the difficulty of isolation of the phosphonate.

A typical procedure for the cyclisation reaction is as follows:
A mixture of of activated ester (0.60 mMol), (prepared by the reaction of equimolar amount of acetyl chloride and thiohydroxamic acid sodium salt with exclusion of light), the telluro-compound, 0.2 mMol in 2 ml of methylene chloride was stirred vigorously under an argon atmosphere. The mixture was irradiated using a 250 W halogen lamp at room temperature for 15 minutes. The course of the reaction was monitored by TLC. If the reaction was not complete after consumption of all the activated ester, a further quantity of ester was added and the reaction mixture irradiated again. This procedure was repeated until all starting material had been converted. The solution was then evaporated *in vacuo* and the residue chromatographed on a short column of silica gel.

Non-activated double bonds of oxime **18** and compound **23** with a terminal olefin, are poor substrates for the tellurium mediated radical addition. Free-radicals generated from these substances are more reactive toward the thiocarbonyl of the *N*-acetoxy-2-thiopyridone than the nucleophilic olefins. After prolonged irradiation only trace amounts of cyclised products **19** and **20** were obtained from the oxime **18**. Olefin **23** gave the non-cyclised thiopyridyl adduct **24** as the only product of the reaction.

This facile synthesis of cyclohexane derivatives by radical cyclisation should be applicable to our programme on the preparation of pseudo-sugars[12].

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