Pergamon

Tetrahedron 54 (1998) 1725–1734

TETRAHEDRON

The Selective Functionalization of Saturated Hydrocarbons. Part 42. Further Studies in Selective Phenylselenation.

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Received 6 October 1997; accepted 23 November 1997

Abstract: An improved procedure for the phenylselenation of saturated hydrocarbons has been developed. The reaction of tributylphosphine with diphenyl diselenide in the presence of Fe^{II} picolinate in pyridine-acetonitrile-trace of water affords a quantitative yield of phenylselenol. Subsequent or prior addition of the saturated hydrocarbon and final addition of 30% hydrogen peroxide gives phenylselenation in excellent yield based on the oxidant added. The mechanism of this reaction has been further studied; carbon and hydroxyl radicals are not part of the mechanism.

INTRODUCTION

Gif Chemistry was originally carried out using a simple iron catalyst in pyridine-acetic acid.[1] Later a crystalline tri-iron complex was isolated.[2] With metallic zinc and oxygen in the same solvent mixture relatively efficient ketonization of saturated hydrocarbons was obtained. This subject has been taken up again recently by Stavropoulos and his colleagues and the various complexes involved have been elegantly characterized.[3]

Whilst the experimental facts have been repeatedly confirmed, it has not been so easy to establish the theory to explain all the data. The concept of the iron-carbon bond was developed from the chemistry of adamantane where tertiary radicals were readily detected by their coupling to pyridine. There was no coupling to the secondary position of adamantane. This was carefully confirmed by the appropriate model studies using tertiary and secondary radicals generated from the appropriate Barton PTOC derivatives.[4] The recent results of Stavropoulos are also in agreement with this.[3]

It was from these observations that the idea of the iron-carbon bond as an intermediate was developed further.[5] During a systematic search for reagents that would capture an iron-carbon bond we added diphenyl diselenide to a Zn^0 iron catalyzed reaction and completely replaced ketonization by an equally efficient phenylselenation of the hydrocarbon.[6] Later, in collaboration with Prof. D.T. Sawyer, it was shown that Fe^{II}-H_2O_2 oxidation of cyclohexane in pyridine-acetic acid gave at first phenylselenation and then, when the iron had been oxidized to Fe^{III} normal ketonization was seen.[7]

After we had recognized that the whole of Gif Chemistry could be explained by two manifolds[8]: Fe^{II}-Fe^{IV} and Fe^{III}-Fe^{V}: it was possible to determine the manifold involved by titration[9] for Fe^{II}. The phenylselenation reaction takes place in the Fe^{II}-Fe^{IV} manifold.[10] Phenylselenol gave higher yields than diphenyl diselenide when Fe^{II}-H_2O_2 was used. The original conditions employed[6] reduced diphenyl diselenide to phenylselenol, as shown by quantitative methylation with methyl iodide.[11] Since phenylselenol is a very efficient trap[12] for carbon radicals we considered that the phenylselenation could not be taking place by a

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PII: S0040-4020(97)10397-0

radical mechanism. Friendly critics[13] have suggested that the phenylselenol is, in fact, completely deprotonated by pyridine or completely complexed by Zn^{II} formed by oxidation of Zn^0. In fact, when H_2O_2 is used in the Fe^{II}-Fe^{IV} manifold,[10] the phenylselenation reaction is still very efficient using preformed phenylselenol. Hence, the complication from Zn^{II} does not apply. As previously cited, phenylselenol was said to be so acidic that it was completely converted to its anion by pyridine.[13] However, the pKa of phenylselenol[14] is 5.9 as compared with the pKa of acetic acid at 4.8 and thiophenol at 6.5. So it would seem improbable that the phenylselenol is extensively deprotonated, particularly in the new procedure reported later, where most of the pyridine has been replaced by acetonitrile.

A further complication is that in the Fe^{II}-Fe^{IV} manifold there is a very fast reaction of Fe^{II} with H_2O_2 to furnish Fe^{IV}=O, or its equivalent cyclic Fe^{II} peroxide. This then reacts with the hydrocarbon with the same selectivity towards adamantane as in the Fe^{III}-Fe^{V} manifold and the same kinetic isotope effect.

With most substrates carbon radicals are then generated and, in the absence of oxygen, can be captured by pyridine.[8] In the presence of phenylselenol these radicals should be reduced back to the hydrocarbon in a nearly diffusion controlled process. This does not happen. Our explanation[10] is that the Fe^{IV} intermediate has phenylselenol and the hydrocarbon ligated to the iron. The product then is formed by ligand coupling.

One further explanation is needed. In the original work using Zn^0 and Fe^{II} the oxidant that couples with Fe^{II} is superoxide[8], as is also established in the electrochemical process, where the cathode keeps Fe^{II} as Fe^{II} and reduces oxygen to superoxide.[15] The reaction with Fe^{II} and superoxide affords Fe^{III}-OOH and leads into the Fe^{III}-Fe^{V} manifold. How then do we descend into the Fe^{II}-Fe^{IV} manifold? In a recent paper[16] we showed that Tempo trapping in the Fe^{III}-Fe^{IV} manifold was due to reduction of Fe^{V} to Fe^{IV} by Tempo which was oxidized to $Tempo^+$ which has its own selectivity of reaction. We presume that phenylselenol also reduces Fe^{V} to Fe^{IV} and thus permits the observed ligand coupling. In the work presented in this paper we are using Fe^{II} + H_2O_2, which is the direct entry into the Fe^{II}-Fe^{IV} manifold.[8]

RESULTS AND DISCUSSION

Previously phenylselenation has given good yields of products with respect to diphenyl diselenide. However, the reactions were relatively inefficient with consideration to the amount of oxidant required. This is true when considering either the Zn^0 or Fe^{II}-H_2O_2 systems. When repeating the reaction under Zn^0-Fe^{II} conditions it was observed that along with the formation of cyclohexylphenyl selenide, diphenyl selenide was also produced. This was confirmed by GC-MS analysis and comparison with an authentic sample. The formation was shown to occur independently of phenylselenation of the hydrocarbon as diphenyl selenide (17%) was formed when cyclohexane was omitted from the reaction mixture. To avoid this unwanted side reaction we studied the reaction using Fe^{II}-H_2O_2, with picolinic acid as the carboxylate ligand. As mentioned earlier[10] the results are much better when phenyl selenol is used instead of the diselenide. This is due in part to the selenol keeping the iron as Fe^{II}. We know that suitable phosphines can reduce disulfides to thiols[17] and as such envisaged that diselenides should behave similarly in the presence of water (Scheme **1**).

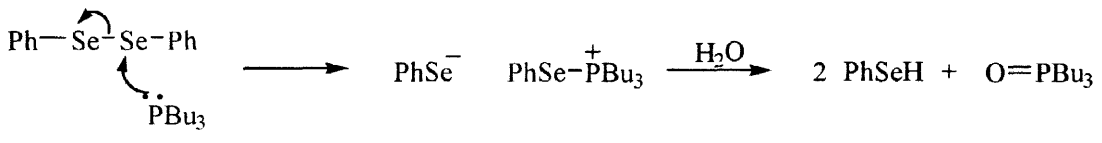
The first reaction was carried out with a catalytic amount of Fe^{II} and sufficient triphenyl phosphine to reduce the diselenide to selenol. These results are shown in Table 1.

Table 1: Effect of PPh_3 on Phenylselenation

Entry	Cyclohexane (mmol)	PhSeSePh (mmol)	PPh_3 (mmol)	H_2O_2 (mmol)	PhSeR (mmol) (%)[a]	Efficiency[b]
1[c]	20	2	2.5	4	1.90 (48%)	48%
2[c]	20	2	2.5	2	0.99 (25%)	50%
3[c]	20	2	4.5	4	1.92 (48%)	48%
4[c]	20	2	6.5	9	3.34 (84%)	37%
5[d]	30	2	8	6	3.95 (99%)	66%

a) Efficiecy with respect to diphenyldiselenide; reductive work up with $Na_2S_2O_4$ gave the same yields indicatiung no oxidation of the product. b) Efficiency is calculated with respect to H_2O_2 assuming 1mmol of H_2O_2.makes 1mmol of PhSeR. c) Reaction carried out in pyridine (30ml). d) Reaction carried out in acetonitrile (30ml) and 4-*t*-butylpyridine (2ml).

Initial reactions carried out in pyridine were complicated by the formation of phenylpyridyl selenide (Entries 1-4). Recently we reported that pyridine could be largely replaced as the solvent by acetonitrile, but the presence of a small amount of a pyridine base was essential.[18] Applied to the present work resulted in no detectable pyridine coupling products. In most cases the efficiencies of the reactions were not greatly enhanced until the addition of the phosphine and hydrogen peroxide was carefully controlled (Entry 5). Hydrogen peroxide was added dropwise to the reaction mixture and upon the onset of a color change (to pale orange from deep red) 2mmol of triphenylphospine was added before addition of hydrogen peroxide was continued. This process was repeated until 6 mmol of hydrogen peroxide was added. At this point only traces of diselenide could be detected by GC and the cyclohexylphenyl selenide was formed almost quantitatively. However, this reaction took over 2h to perform. It was shown that the yields were less when the hydrogen peroxide was added in one portion, or when there was a large excess of phosphine present. Reaction with either the phosphine, the selenol, the selenide or all these compounds could explain this. The reaction of hydrogen peroxide with Fe^{II}, however, must be faster than the alternative reactions. In order to confirm that phenyl selenol was formed under the reaction conditions, we generated the selenol in the presence of Fe^{III} which was rapidly reduced to Fe^{II}.



Scheme 1

The addition of triphenylphosphine to a solution of Fe^{III} and diphenyl diselenide gave 60% of Fe^{II} after 4h indicating that the formation of selenol was slow. However, when tributyl phosphine was substituted for triphenyl phosphine, all the Fe^{III} was reduced to Fe^{II} after 2min as determined by spectroscopic analysis.[9] This confirms that we are operating within the Fe^{II}-Fe^{IV} manifold. We also studied the reaction of the phosphines with the diselenide by ^{31}P and ^{77}Se nmr spectroscopy. With triphenyl phosphine the reaction was slow with only traces of the derived oxide detected after 2h. The oxide of tributyl phosphine was formed much faster. By selenium nmr we clearly detected the formation of phenyl selenol by the appearance of a peak resonating at 151ppm and the disappearance of the diselenide resonating at 475ppm.[14] A final proof of the presence of phenyl selenol under the reaction conditions was shown by the addition of methyl iodide to a solution of the diselenide, tributyl phosphine and Fe^{II}. This gave phenyl methyl selenide in high yield. These experiments confirmed that in the presence of a small excess of tributylphosphine the iron will be Fe^{II} and we will have only phenyl selenol. The results are collated in Table 2.

As expected under defined conditions the formation of the cyclohexylphenyl selenide was efficient with respect to both hydrogen peroxide and diphenyl diselenide (Entry 1). The rate of addition of hydrogen peroxide was important, as indicated by Entry 2, but not as crucial as previously observed with triphenyl phosphine. The hydrogen peroxide was added over 10 seconds in Entry 1 of Table 2. The reaction is dependent upon the appropriate carboxylate ligand (Entry 3) and also the concentration of the hydrocarbon (Entries 4-7). However, the amount of iron added has little effect on the reaction (Entries 8 and 9). When more than 1mmol of phenylselenol was present from the start of the reaction the efficiencies dropped from 85% to ~33 and 41% (entries 10 and 11). This was believed to be due to competition for hydrogen peroxide between Fe^{II} and selenol, which is readily oxidized back to the diselenide. The yield of the product was increased by adding 1mmol of tributyl phosphine to the solution after the reaction mixture changed color from red to orange. This resulted in the color changing back to red (Fe^{II}) and hydrogen peroxide addition was continued. After 4mmol of phosphine and 5.4mmol of hydrogen peroxide, most of the phenylselenol (85%) had reacted (Entry 12). To ensure phenylselenol was still present during the addition of hydrogen peroxide, methyl iodide was added after the addition of 0.5 mmol of oxidant. The efficency was still 80% with respect to hydrogen peroxide and 0.18mmol of methyl phenylselenide was found confirming that selenol was still present (Entry 13). In the appropriate blank experiment we found that diphenyl diselenide could not be methylated except in trace amounts, to give methyl phenyl selenide (0.01mmol). The best conditions for making larger amounts of product were found to be the addition of 0.5mmol of diselenide and 0.75mmol of phosphine to the reaction mixture as the color changed before addition of hydrogen peroxide was continued. After four cycles had been completed an over all efficiency of 72% for both hydrogen peroxide and diselenide were obtained (Entry 14).

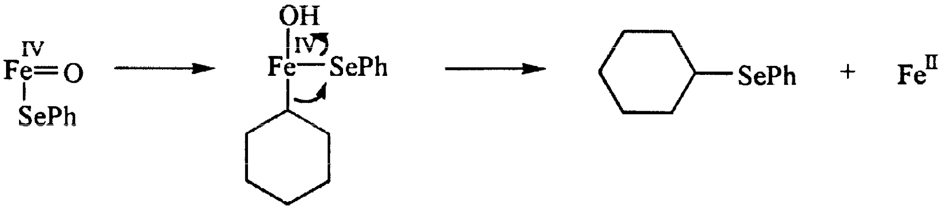
Table 2: Phenylselenation with PhSeSePh/PBu_3[#]

Entry	Cyclohexane (mmol)	PhSeSePh (mmol)	PBu_3 (mmol)	H_2O_2 (mmol)	PhSeR (mmol)	Efficiency*
1	30	0.5	0.75	1	0.89	89%
2	30	0.5	0.75	1[a]	0.49	49%
3[b]	30	0.5	0.75	1	0.05	5%
4[c]	5	0.5	0.75	1	0.32	32%
5[c]	10	0.5	0.75	1	0.53	53%
6[c]	15	0.5	0.75	1	0.74	74%
7[c]	20[d]	0.5	0.75	1	0.52	52%
8[e]	30	0.5	0.75	1	0.83	83%
9[f]	30	0.5	0.75	1	0.71	71%
10	30	2	4	4	1.32	33%
11	30	2	4	4.9	2.02	41%
12[g]	30	2	4	5.4	3.40	63%
13[h]	30	0.5	0.75	0.5	0.4 $PhSeCH_3$ 0.18	80%
14	30	2	6.5	4.9	3.53	72%
15[i]	30	0.5	0.75	1	0.82	82%
16[j]	30	0.5	0.75	1	0.07	7%
17[k]	30	0.5	0.75	1	0.15	15%

Reactions were carried out with $FeCl_2$ (0.25mmol) and picolinic acid (0.75mmol) in CH_3CN (30ml) and 4-*t*-butylpyridine (2ml) under argon unless otherwise stated. * Efficiency was calculated with respect to H_2O_2. a) H_2O_2 was added in one portion. b) Picolinic acid was omitted. c) Reaction carried out in CH_3CN (15ml) and 4-*t*-butylpyridine (1ml). d) Solution was heterogeneous. e) 0.5mmol of Fe^{II}. f) 0.5mmol of Fe^{II}. g) 1mmol of PBu_3 was added when the color changed from red to orange. h) After addition of H_2O_2, methyl iodide (5eq.) and *t*-butyltetramethylguanidine (5eq.) were added. i) Addition of 5mmol of TFA. j) Addition of 5mmol of *t*-butyltetramethylguanidine. k) Addition of 5mmol of triethylamine.

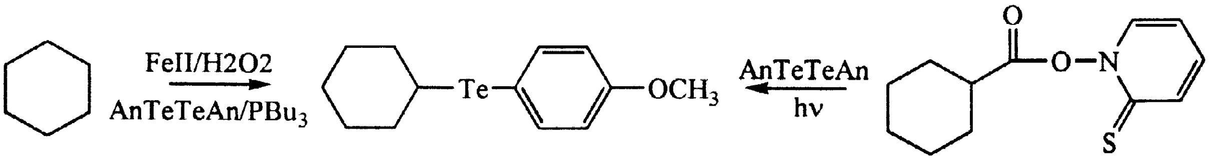
As mentioned above the proposal that the phenylselenol is converted completely to its anion in pyridine is not justified by the known pKa values. Removal of most of the pyridine in the latter experiments makes this proposal even less likely. However, in order to make quite sure, we added 5mmol of trifluoroacetic acid (Entry 15). The reaction proceeded with its usual (82%) efficiency. In contrast, the addition of 5mmol of t-butyltetramethylguanidine, a base strong enough to convert the phenylselenol to its anion, [19] gave only a 7% yield (Entry 16). Substituting triethylamine for t-butyltetramethylguanidine gave only slighlty more product (Entry 17). Furthermore in the ^{77}Se nmr studies, which demonstrated the complete conversion of diphenyl diselenide to phenylselenol, there was no indication of a further signal for the selenide anion.[20]

Phenylselenol is an excellent trap for carbon radicals[12] and even more so for hydroxyl radicals. So the previous discussion of mechanism[10] can be abbreviated. The carbon radicals usually seen in the Fe^{II}-Fe^{IV} manifold by fragmentation of the Fe^{IV}-carbon bond cannot be present. Hence the ligand coupling mechanism (Scheme **2**) that we preferred earlier[10] must be correct. This must reflect the nature of the Fe^{IV}-SePh bond. The matter merits the attention of computational chemists.



Scheme 2

As tellurium is the next element in the chalcogen series, it seemed possible that this methodology could be extended to the synthesis of tellurium analogues from ditellurides. As postulated, we found that replacing diphenyl diselenide with dianisyl ditelluride, under the optimum conditions for selenide formation, gave the 4-anisyl cyclohexyl telluride in 50% yield. The product was identified by comparison with an authentic sample[21] prepared from the cyclohexyl Barton PTOC ester and the ditelluride (Scheme **3**).

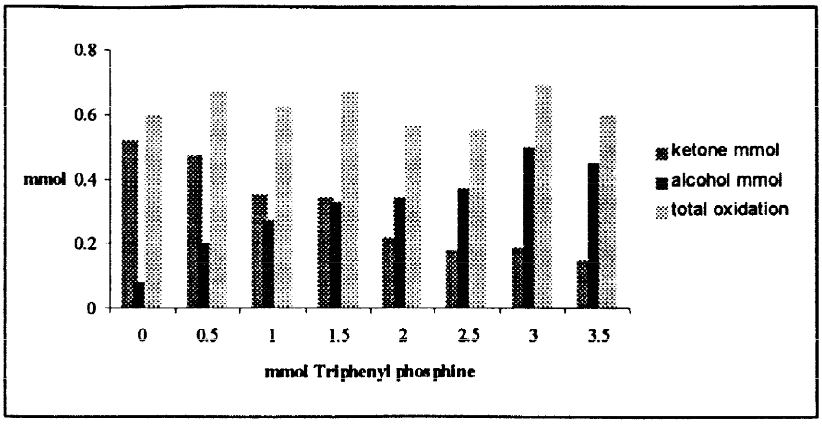


AnTeTeAn = Dianisyl ditelluride

Scheme 3

The results in this paper confirm that carbon or oxygen radicals are not involved in the phenylselenation of saturated hydrocarbons. They are also a perfect example of the Gif Paradox[5], namely that saturated hydrocarbons are oxidized in preference to a far more easily oxidized substrate, phenylselenol. Our explanation for these anomalies remains the same, namely that the saturated hydrocarbon, activates, and immediuatley reacts with an iron species that has its oxidizing power initially in a relatively inactive form (The Sleeping Beauty[5]).

In an earlier paper we had shown that triphenylphosphine did not interfere in the Zn^0-Fe^{II} reaction until after the formation of the derived hydroperoxide[20], the precursor of the ketone. It reduced selectivley the hydroperoxide to alcohol, but the total amount of ketone and alcohol was constant over a wide wariation of triphenylphosphone concentrations. We have confirmed the accuracy of these observations (Figure 1).



$FeCl_2.4H_2O$ (0.25mmol), Zn (20mmol), Cyclododecane (5mmol), Triphenyl phosphine (Xmmol), acetic acid (2.3ml) and pyridine (28ml).

Figure 1

EXPERIMENTAL

Unless otherwise stated, all solvents and chemicals were, after verification, used as received. Anisyl cyclohexyl telluride was prepared by normal literature methods.[21] Hydrogen peroxide was used as a 30% solution in water. ^{77}Se nuclear magnetic resonance spectra were performed on a Varian XL-200 Broad Band Spectrometer. Chemical shifts were reported with respect to diphenyl diselenide (δ = 475ppm[14]).Gas chromatographic analyses were carried out on a Hewlett Packard 5890 series II gas chromatograph fitted with a precolumn. Columns used were DB-wax (30 m, 0.32 mm i.d., 25 mm film thickness), DB-5 (30 m, 0.32 mm i.d., 25 mm film thickness) or DB-1 (15 m, 0.32 mm i.d., 25 mm film thickness) capillary columns from J&W Scientific. Gas chromatography-mass spectrometry (GC-MS) analysis was carried out on a Hewlett Packard 5890 series II gas chromatograph coupled with a Hewlett Packard 5971 series quadropole mass-selective detector (40 eV, electron impact). Helium was used as the carrier gas. The column used in the GC-MS was a HP-5MS (30 m, 0.25 mm i.d., 0.25 mm film thickness).

Known compounds were identified by comparison with authentic samples

General work up procedure for quantification of products by GC is as follows: An aliquot of the reaction mixture (1ml) was added to a solution of naphthalene (1ml). Water (5ml) was added and the mixture was extracted with ether (10ml). The extracts were dried ($MgSO_4$) and the products quantified by gas chromatography.

Phenylselenation of cyclohexane in the presence of triphenyl phosphine.

A solution of $FeCl_2.4H_2O$ (50mg, 0.25mmol), picolinic acid (93mg, 0.75mmol) diphenyldiselenide (624mg, 2mmol), cyclohexane (3.24ml, 30mmol) and 4-*t*-butylpyridine (2ml) in acetonitrile (30ml) was prepared under an atmosphere of argon and cooled to 0° with an ice bath. Triphenyl phosphine (656mg, 2.5mmol) was added and the mixture stirred for 5min. Hydrogen peroxide was added dropwise to the red solution at which time the color fades and then returns before further addition. Upon persistence of the pale color a portion of triphenyl phosphine (262mg, 1mmol) was added and the solution stirred for 10min. Addition of hydrogen peroxide (6mmol of H_2O_2) to the red solution was continued and the process repeated until all the diphenyl diselenide was consumed as indicated by GC analysis after a general work-up.

Reduction of Fe^{III} by diphenyldiselenide/tributylphosphine.

Tributyl phosphine (250µl, 1mmol) was added to a mixture of $FeCl_3.6H_2O$ (135mg, 0.5mmol), picolinic acid (165mg, 1.25mmol), diphenyldiselenide (312mg, 0.1mmol) and 4-*t*-butylpyridine (1ml) in acetonitrile (15ml). After 2min an aliquot was taken and the amount of Fe^{II} determined by the method of Clark.[9] Analysis found that all the Fe^{III} has been converted to Fe^{II}.

Detection of phenylselenol by ^{77}Se-NMR spectoscopy

Tributyl phosphine (380µl, 1.5mmol) was added to a solution diphenyl diselenide (312mg, 1mmol) in acetonitrile (2.25ml) under an atmosphere of argon in a 10mm nmr tube. A drop of water was added and the solution left at room temperature for 1h before acquiring the nmr. ^{77}Se-NMR (CH_3CN) δ : 152, (s).

Methylation of phenylselenol under the reaction conditions.

Tributyl phosphine (190µl, 0.75mmol) was added to a mixture of $FeCl_2.4H_2O$ (50mg, 0.25mmol), picolinic acid (92mg, 0.75mmol), diphenyldiselenide (156mg, 0.5mmol) and 4-*t*-butylpyridine (2ml) in acetonitrile (30ml). After 5min methyl iodide (310µl, 5mmol) was added and the solution stirred for 1h. The mixture was poured into water and extracted with diethyl ether (2x25ml). The extracts were washed with dil. HCl (2x10ml), dried and the solvent evaporated to give methyl phenylselenide in 60% yield.

General procedure for the phenylselenation of cyclohexane in the presence of tributylphosphine.

$FeCl_2.4H_2O$ (50mg, 0.25mmol), picolinic acid (93mg, 0.75mmol), diphenyldiselenide (156mg, 0.5mmol), tributylphosphine (190µl, 0.75mmol) and cyclohexane (3.24ml, 30mmol) were dissolved in a mixture of 4-*t*-butylpyridine (2ml) and acetonitrile (30ml) under an atmosphere of argon. The mixture was cooled to 0° in an ice bath for 5min at which time hydrogen peroxide (1mmol) was added dropwise over 10sec. A general work-up procedure was followed and the products quantified by gas chromatography.

Methylation of excess phenyl selenol after phenylselenation.

$FeCl_2.4H_2O$ (50mg, 0.25mmol), picolinic acid (93mg, 0.75mmol), diphenyldiselenide (156mg, 0.5mmol), tributylphosphine (190µl, 0.75mmol) and cyclohexane (3.24ml, 30mmol) were dissolved in a mixture of 4-*t*-butylpyridine (2ml) and acetonitrile (30ml) under an atmosphere of argon. The mixture was cooled to 0° in an ice bath for 5min at which time hydrogen peroxide (0.5mmol) was added dropwise over 10sec. t-Butyltetramethylguanidine (244µl, 5mmol) was added to the solution followed by methyl iodide (310µl, 5mmol) and the mixture stirred for 40min. An aliquot was taken and after a general work up the products were quantified by GC analysis to give cyclohexyl phenyl selenide (0.42mmol) and methyl phenyl selenide (0.18mmol).

Attempted methylation of diphenyl diselenide.

$FeCl_2.4H_2O$ (50mg, 0.25mmol), picolinic acid (93mg, 0.75mmol), diphenyldiselenide (156mg, 0.5mmol), and cyclohexane (3.24ml, 30mmol) were dissolved in a mixture of 4-*t*-butylpyridine (2ml) and acetonitrile (30ml) under an atmosphere of argon. t-Butyltetramethylguanidine (244µl, 5mmol) was added to the solution followed by methyl iodide (310µl, 5mmol) and the mixture stirred for 150min. After general work up GC analysis showed only a trace methyl phenyl selenide (0.01mmol) and unreacted diselenide.

Reaction of Diphenyl diselenide under Zn^0-Fe^{II} conditions.

Diphenyl diselenide (624mg, 2mmol) was added to a rapidly stirred suspension of zinc dust (1.3g, 20mmol) in a mixture of $FeCl_2 .4H_2O$ (50mg, 0.25mmol) and acetic acid (2.3ml) in pyridine (28ml). After consumption of the zinc (~45min) and aliquot was taken and the products determined by GC analysis. Diphenyl selenide was formed in 17% yield.

Synthesis of 4-anisyl cyclohexyl telluride.

$FeCl_2.4H_2O$ (50mg, 0.25mmol), picolinic acid (93mg, 0.75mmol), dianisyl ditelluride (235mg, 0.5mmol), tributylphosphine (190µl, 0.75mmol) and cyclohexane (3.24ml, 30mmol) were dissolved in a mixture of 4-*t*-butylpyridine (2ml) and acetonitrile (30ml) under an atmosphere of argon. The mixture was cooled to 0° in an ice bath for 5min at which time hydrogen peroxide (0.5mmol) was added dropwise over 10sec. An aliquot was taken and after a general work up the products quantified by GC analysis. 4-Anisyl cyclohexyl telluride was formed in 50% yield (0.5mmol).

ACKNOWLEDGMENTS

We thank the Welch Foundation, Unilever Ltd. and the Schering Plough Coraration for the support of this work. We also thank Dr. Richard Vonder Embse for performing the ^{77}Se NMR spectroscopy.

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