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A Novel and Highly Efficient Synthetic Route to Unsymmetrical Organoselenides Using Cesium Bases

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Received February 4, 2004

Abstract: A new and convenient one-pot method for the preparation of unsymmetrical selenides has been developed. In the presence of cesium hydroxide, molecular sieves, and DMF, benzeneselenol undergoes direct alkylation with various alkyl halides for the synthesis of alkyl phenyl selenides in moderate to excellent yields. Another method to prepare unsymmetrical organoselenides was also completed by coupling terminal alkynes with benzeneselenyl bromide. As an application, the synthesis of a selenopeptide was also accomplished. Furthermore, this methodology was extended to the synthesis of an organoselenide on solid support.

Organoselenium chemistry has continued to attract considerable attention due to its pivotal role in the synthesis of a large number of biological compounds (e.g., selenocarbohydrates, selenoamino acids, and selenopeptides). Additionally, organoselenium compounds have emerged as an exceptional class of structures that exemplify a role in biochemical processes, serving as important therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplements.[1] Moreover, synthetic alkyl phenyl selenides serve as crucial synthons in the transformations of a variety of functional groups.[2] Unfortunately, most of the work performed in this area is highly problematic due to the instability of these compounds in air and moisture, as well as their sensitivity to strongly acidic and basic reaction media. Despite considerable progress toward the synthesis of organoselenides, typically, diorganyl selenides still remain the reagents of choice.[3] However, multistep procedures are required in order to obtain the title compounds.[4] Although this classical method may prove the most popular route at this time,[3] considerable efforts have been equally devoted to one-step preparations employing arylselenotrimethylsilanes.[5] Alternative methods involve the condensation of alcohols with selenols in the presence of acid.[6] In this context, the most direct approach toward the synthesis of organoselenides is the direct alkylation of an alkyl halide employing the synthetic intermediate, the selenolate anion, which is by far a more potent nucleophile than its sulfur counterpart.[7] As a drawback, most of these synthetic protocols elaborated upon above suffer from lengthy synthetic steps and harsh reaction conditions and often require the use of specialized reagents which are often difficult to obtain.[8] Taking into account these constraints, we were motivated to investigate the development of a mild, more convenient, and efficient reaction condition for the synthesis of unsymmetrical organoselenides which circumvented these common impediments.

Recently, during our studies toward cesium-promoted P- and N-alkylations, we reported a mild procedure for the synthesis of tertiary[9] and ditertiary phosphines[10] and monohydroxyphosphines[11] using CsOH as the base. Inspired by these studies, we have also disclosed efficient synthetic protocols for the formation of phosphonates,[12] phosphonodithioformates,[13] carbazates,[14] and dithiocarbazates,[14] respectively, using Cs_2CO_3 and tetrabutylammonium iodide. More recently, we have launched our research efforts toward identifying novel applications of the "cesium effect"[15] as well as the nascent synthesis of selenopeptides. In regard to the similarities between sulfur and selenium, we decided to first embark on the preparation of unsymmetrical organoselenides using our

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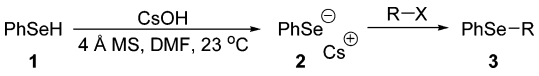
10.1021/jo0401265 CCC: $27.50
Published on Web 05/11/2004

SCHEME 1



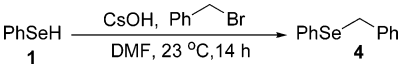
cesium-promoted alkylation procedures, which we disclose in this paper. However, our chemoselective alkylation of thiols using cesium bases will be reported soon.

Toward this objective, and building upon our preliminary studies,[9−14] we decided to explore the preparation of unsymmetrical selenides via an innovative strategy. As illustrated in Scheme 1, under a dry nitrogen atmosphere, in the presence of powdered 4 Å molecular sieves[16] and cesium hydroxide, it appeared tenable that benzeneselenol (**1**) undergoes rapid deprotonation in anhydrous *N*,*N*-dimethylformamide (DMF) as the solvent of choice, affording the in situ benzeneselenolate anion (**2**).[17] After the mixture was stirred for 1 h at room temperature, an orange suspension resulted. Subsequent addition of the alkyl halide generates a pale yellow solution, which produces the desired unsymmetrical selenide **3** exclusively in high yields after workup and purification. Usually, benzeneselenol is highly labile and easily oxidized in air forming diphenyl diselenides; however, this was not the case employing our reaction conditions. As a direct comparison, a survey of solvents was screened. Polar aprotic solvents including HMPA, DMSO, NMP, THF, and CH_3CN were found to be acceptable solvents, whereas other media encompassing CH_3OH, hexane, EtOAc, CH_2Cl_2, etc. were not optimal. This "naked anion" **2**, which is weakly coordinated to the cesium cation, as extensively described by the "cesium effect",[15] reacted efficiently at ambient temperature to generate numerous unsymmetrical selenides **3** in high yields. It is important to highlight that, using our conditions, we were not troubled by the foul smell of **1** or the formation of any byproducts. Furthermore, the rapid conversion of the anion **2** to the corresponding diselenide in the presence of air was circumvented.

Nevertheless, in our preliminary investigations aimed at the preparation of **4**, we undertook a detailed study using benzeneselenol (**1**) and benzyl bromide (**11**) as model coupling partners in order to probe the proper reaction conditions with respect to various bases. Notably, cesium hydroxide monohydrate was the judicious base of choice, delivering benzyl phenylselenide (**4**) exclusively, in very high yield and purity (entry 5). On the other hand, other alkali metal hydroxides including lithium, sodium, potassium, and rubidium hydroxide, under the same procedure, offered low conversion of **1** (entries 1−4). We attribute this high yield as further evidence of the "cesium effect",[15] which to our knowledge, has not been extended to include the alkylation of selenols. Encouraged by these results, a direct comparison was made using other cesium bases. For example, three equivalents of cesium carbonate afforded **4** in a moderate yield (entry 6). Interestingly, addition of an additive such as tetrabutylammonium iodide (TBAI) was beneficial offering a higher product yield under the same conditions (entry 7). As further proof of viability, organic bases encompassing Et_3N and DBU were also found to be completely ineffective. In contrast, an attempt to use another base (LDA) (entry 10) gave rise to similar results to entry 6. Finally, KO^{t}Bu (entry 11) proved completely unsuccessful to afford only a trace amount of desired product **4** (Table 1). As a direct comparison to our cesium-promoted Se−C bond formation, benzyl phenyl selenide (**4**) was formed via a previously reported protocol.[18] For example, diphenyl diselenide was reduced using $NaBH_4$ to the corresponding sodium phenylate selenoate anion which underwent alkylation using benzyl bromide to afford **4** in a lower yield (74%) when compared to our method. Thus, our methodology is clearly operationally simpler and more efficient.

Next, a wide spectrum of halides was screened in order to evaluate the scope, limitations, and practicality of the reaction procedure. As delineated in Table 2, numerous primary halides were examined and found to be highly effective to the newly developed cesium hydroxide promoted selenium alkylation techniques. Results described in Table 2 show that unsymmetrical selenides can be obtained in moderate to excellent yield and in high purity. For example, primary activated halides such as methyl iodide (**5**) and bromoethane (**7**) reacted expedi-

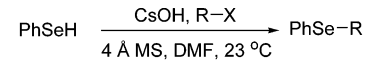
TABLE 1. Alkylation of Benzeneselenol Using Various Bases



entry	base	yield[a] (%)	entry	base	yield[a] (%)
1	LiOH	26[b]	7	Cs_2CO_3/TBAI	76[c,d]
2	NaOH	65[b]	8	Et_3N	51
3	KOH	72[b]	9	DBU	25
4	RbOH	74[b]	10	LDA	57
5	CsOH	94[b]	11	KO^{t}Bu	trace
6	Cs_2CO_3	57[c]			

[a] Isolated yield. [b] Activated 4 Å molecular sieves were added. [c] 3 equiv were used. [d] 3 equiv of tetrabutylammonium iodide was added.

TABLE 2. Synthesis of Unsymmetrical Diselenides Using Primary Alkyl Halides



entry	halide (RX)	RSePh	time (h)	yield (%)
1	MeI (**5**)	PhSeMe (**6**)	5.5	quant.
2	EtBr (**7**)	PhSeEt (**8**)	10	quant.
3	Br (**9**)	SePh (**10**)	9	95
4	Ph Br (**11**)	Ph SePh (**4**)	14	94
5	Br (**12**)	SePh (**13**)	12	89
6	C_7H_{13} I (**14**)	C_7H_{13} SePh (**15**)	28	83
7	$C_{10}H_{19}$ Cl (**16**)	$C_{10}H_{19}$ SePh (**17**)	28	69
8	$C_{11}H_{23}$ Br (**18**)	$C_{11}H_{23}$ SePh (**19**)	19	97

(16) When molecular sieves were not activated, product yields diminished with recovery of **1** predominantly.

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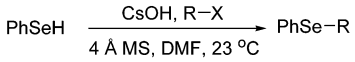
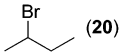
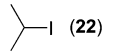
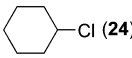
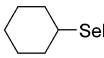
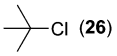
TABLE 3. Unsymmetrical Organoselenide Formation Using Secondary and Tertiary Halides in the Presence of CsOH

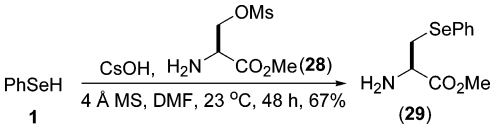


entry	halide (RX)	RSePh	time (h)	yield (%)
1	 (**20**)	 (**21**)	18	88
2	 (**22**)	 (**23**)	18	77
3	 (**24**)	 (**25**)	34	78
4	 (**26**)	 (**27**)	34	trace

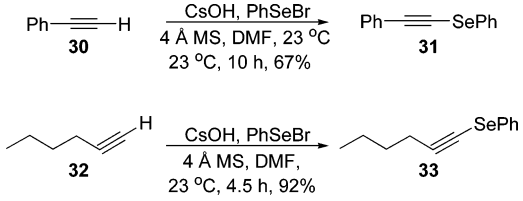
ently to yield the corresponding methyl and ethyl phenyl selinides (**6** and **8**) in quantitative yields (entries 1 and 2). Upon noting this exciting result, the reaction was then attempted with other activated halides including allyl bromide (**9**) and benzyl bromide (**11**), which generated allyl (**10**) and benzyl phenyl selenide (**4**), respectively, in outstanding yields (entries 3 and 4). In the case of crotyl bromide (**12**), allylic phenyl selenides were formed in 89% yield as a mixture of regioisomers after 12 h (entry 5). Next, aliphatic primary halides containing longer alkyl chains also proved successful leading to the synthesis of several unique unsymmetrical selenides. As delineated in entries 6 and 7, *n*-octyl iodide (**14**) and 1-chlorounde-cane (**16**) were treated with PhSeH (**1**) to form the corresponding products **15** and **17** after the same time period. Remarkably, 1-bromododecane (**18**), a lipophilic bromide, transformed into unsymmetrical selenide (**19**) in impressive yield (entry 8). Once again, these results further indicate that our methodology, when compared to conventional techniques, holds significant advantages in terms of mild reaction conditions and higher product yields.[8a]

Our attention was next turned to structurally diverse unsymmetrical selenides. To demonstrate the efficiency and scope of the present method, we shifted our attention toward the Se-alkylation of **1** using secondary and tertiary halides. Therefore, additional experiments were performed to examine the influence of the correspond-ing halides. Although the synthesis of unsymmetrical branched alkyl chains and cyclic ring structures usually requires elevated temperature to complete the desired transformations, this proved unnecessary in our studies. As demonstrated in Table 3, an examination of secondary and tertiary bromides was accomplished for complete substrate viability. It was gratifying that 2−bromobutane (**20**) efficiently coupled with **1** after 18 h to produce the secondary alkyl phenyl selenide in 88% yield (**21**) (entry 1). As depicted in entries 2 and 3, similar trends were observed. For example, upon reaction of **1** with 2−iodo-propane (**22**) isopropyl selenobenzoate (**23**) was formed after 18 h. Interestingly, cyclohexyl phenyl selenide (**25**) formed in 78% yield from the reaction of **1** with cyclohexyl chloride (**24**) giving nearly similar product yields. In each case, elimination products were not detected in any study. Product yields again, were found to be greater than previously reported methods.[8a] As anticipated, we next

SCHEME 2



SCHEME 3



sought to synthesize a tertiary alkyl phenyl selenides, such as **27**. For example, *tert*-butyl chloride (**26**) was found to be completely unreactive.

Due to their potential biological activity over recent years, there has been a surge of attention given to biologically active selenium-containing amino acids (se-lenopeptides) such as L-selenocysteine and L-lanthionine selenium peptides.[19] In this context, a formidibale chal-lenge still remains to develop novel synthetic methods that can permit the introduction of selenium into opti-cally active amino acids, which could be wideley explored as critical metabolites in cancer chemoprevention.[20] With this consideration in mind, we next focused our attention to the use of our methodology in order to synthesize a selenopeptide employing our cesium-base Se-alkylation procedure. This route may constitutute an attractive option for the preparation of various structurally diverse selenopeptides in the future. To put our methodology into full potential, we envisaged the application of our condi-tions to the preparation of a modified selenopeptide (selenocysteine) derived from L-serine as the starting ma-terial. Replacment of the HS-group of cysteine may play an important role in the protection of organisms from the destructive activity of hydroperoxidases.[21] Analogous to the above techniques, as a representative example, serine methyl ester hydrochloride (**28**) was transformed into the corresponding mesylate,[22] and subsequently coupled with chiral building block **28** with **1** which proved to be an advantageous way to furnish selenopeptide **29** in 67% yield after 48 h with accompaniment of starting material **28** (Scheme 2). It is noteworthy to mention competing side products stemming from elimination or ester sa-ponification were not detected.[23] Having succcessfully installed motif **28** into **1**, subsequent hydrolysis of the methyl ester of **29** would be a convenient way to generate a selenocysteine derivative. Keeping in mind the cleavage of the C−Se bond of phenylselenide is a difficult route to provide L-selenocysteine directly from **29**, modifications of this route are currently underway.

In addition to the synthetic improvement, our standard approach also holds an important advantage in the

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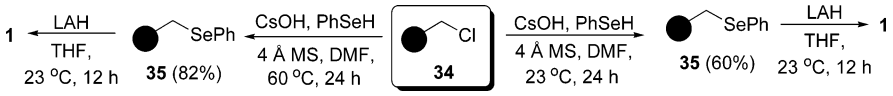
(23) ^{1}H NMR, ^{13}C NMR, and 2D NMR analyses indicate the product as a single product and high purity.

SCHEME 4



synthesis of alkynyl selenides. To determine the reaction flexibility, we next sought to determine if our selenenation reaction was found to be successful upon switching reaction partners employing terminal acetylenes in the presence of phenyl selenyl bromide (Scheme 3). Recently, cesium hydroxide proved to be a superior base for the catalytic alkynylations of aldehydes, ketones and nitriles.[24] In contrast, Corey's protocol, utilizes CsOH in stoichiometric amounts as a base in phase−transfer alkylations.[25] Keeping this attractive protocol in mind, we decided to utilize a similar, but modified version for the preparation of various unsymmetrical selenides that contain the acetylide functionality. We found that treatment of phenylacetylene (**30**) with a catalytic amount of $CsOH·H_2O$ (~20 mol %) successfully coupled to PhSeBr in DMF within 10 h at room temperature. The desired selenoalkyne (**31**) was isolated after workup and purification in a prosperous 67% yield. Finally, 1-hexyne (**32**), a terminal alkyne, also proved feasible to give alkyne **33**.

Accordingly, in an effort to extend the scope and significance of our organoselenium chemistry, we have also carried out a practical synthesis of an unsymmetrical selenide on a polymer support. Since the first organoselenium resin was reported in 1976,[26] several groups have developed support-bound organoselenium resins as synthetic intermediates and convenient linkers.[27,28] The selenium−carbon bond is stable under a broad variety of reaction conditions, but can selectively be cleaved by tin radicals or by oxidants. Therefore, new linkage strategies with various loading and cleavage protocols make the selenium moiety popular for further functionalization. In turn, other methods have been reported using alkyl metal selenides.[29] In addition, electrophilic selenium derivatives undergo addition to alkenes under mild reaction conditions. Polystrene-bound aryl styrene aryl selenium derivatives have also been prepared from lithiated polystyrene and metallic selenium[30] or dimethyldiselenide.[31] These corresponding derivatives are suitable starting materials for the preparation of other selenium reagents, which enable for the facile attachment of organic substrates to insoluble support. However, little work has been accomplished in this field and future studies would attract much interest. Using a protocol similar to our solution-phase strategies, the derivatization of **1** to **35** provided a versatile method for the synthesis on selenides on solid support. As demonstrated in Scheme 4, two reaction temperatures were examined. In the presence of Cs_2CO_3 (6 mmol) and TBAI (6 mmol), and **1** (6 mmol) smoothly united to Merrifield's peptide resin **34** (2 mmol) at room temperature to afford the resin-bound phenylselenide **35** product in 60% yield. However, in an attempt to achieve better results a higher temperature (60 °C) produced the polymer-bound selenide **35** in higher yield (82%). To address issues of product identity and purity utilizing our solid-phase procedure, the resulting resin-bound selenide (**35**) was verified by infrared spectroscopy (KBr pellet) and was then cleaved using LAH to return the starting benzeneselenol (**1**) cleanly after 12 h in high yield. It is important to highlight that crude NMR spectra of the cleaved products were clean and no other side products were noticed within our detection limits.[32] In the future, we plan to investigate the efficient synthesis of unsymmetrical selenides, selenopeptides, as well as the development of novel selenium linkers as a scaffolding in the construction of functional groups on solid support. Further applications will be disclosed in due course in the format of a full paper.

In summary, a novel, one-pot, mild, and practical approach for the synthesis of unsymmetrical selenides has been developed. In the presence of benzeneselenol, molecular sieves, cesium hydroxide, and DMF, various electrophiles coupled for the useful preparations of unsymmetrical primary and secondary alkyl phenyl selenides exclusively. Furthermore, an amino acid derivative was successfully employed to generate a selenopeptide. Also, various terminal alkynes smoothly coupled with phenylselenyl bromide to produce unsymmetrical terminal selenides. In addition to the preceding results, we also established a cesium-promoted, one-step coupling of Merrifield's resin with benzeneselenol in the presence of Cs_2CO_3 and TBAI leading to the exclusive synthesis of unsymmetrical selenides on solid support.

Acknowledgment. Financial support from the National Science Foundation−Kentucky EPSCoR (596166) is gratefully acknowledged, as is support from Western Kentucky University. Also, we sincerely thank Chemetall for their generous supply of cesium bases. R.N.S. dedicates this paper to the memory of Mrs. Mary T. Salvatore.

Supporting Information Available: Experimental procedures and spectral and analytical data for all products. Selected IR and the GC/MS for **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0401265

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(32) Infrared spectra of resin-bound organoselenide products **35** were taken as a KBr pellet. The yields for the reactions were calculated based on loading for the selenide after drying in vacuo over a 24 h time period. Also, **35** was converted to **1** cleanly (80−85% recovered isolated yield), which was compared to the authentic samples by NMR analysis for identity and purity.