Rapid and precise preparation of reactive benzeneselenolate solutions by reduction of diphenyl diselenide with hydrazine– sodium methanolate

Lars Henriksen* and Nicolai Stuhr-Hansen

Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark. E-mail: larsh@kiku.dk

Received (in Cambridge) 7th May 1999, Accepted 14th June 1999

Solutions of sodium benzeneselenolate sufficiently reactive to effect aromatic substitution and ester dealkylation are prepared in DMSO or NMP from diphenyl diselenide and hydrazine hydrate by titration with methanolic sodium methanolate.

The benzeneselenolate ion (1) is a powerful nucleophilic species which, apart from its utilization in the construction of selenium containing materials, has a wide range of applications as a tool in organic synthesis.¹ Since benzeneselenol is an obnoxious and highly oxygen-sensitive substance the simple deprotonation route to 1 is impractical and solutions of 1 are usually generated by *in situ* reduction of the stable and less volatile diphenyl diselenide (2). Compound 2 is readily reduced and several reagents have been used for this purpose.² The reduction with sodium tetrahydroborate³ is the most commonly used procedure. However, this preparation gives 1 as a boron complex with diminished nucleophilic reactivity.⁴ Reactive solutions of 1 have been prepared from 2 by reduction with alkali metals⁴ or alkali metal hydrides⁵ in an inert solvent.

The reduction of **2** with a combination of hydrazine and sodium hydroxide has been accomplished using an excess of the reagents.⁶ We have found that the reduction of **2** with hydrazine hydrate proceeds almost instantaneously at room temperature in DMSO (or similar solvents) upon addition of a concentrated (~5 M) solution of sodium methanolate in methanol to give a homogeneous solution of **1** (Scheme 1a).

2 PhSeSePh +
$$N_2H_4$$
 + 4 MeO⁻ \longrightarrow 4 PhSe⁻ + N_2 + 4 MeOH a)
2 1

$$N_2H_4 + O_2 \xrightarrow{PhSe^-} N_2 + 2 H_2O$$
 b)

Scheme 1

The reaction can be carried out as a colorimetric titration with a sharp end-point (yellow to colorless) to produce a solution containing a precisely defined amount of **1** which is free of excess base. Only the equivalent amount of hydrazine is needed but we prefer a slight (10-20%) excess in order to ensure that the methanolate ion is the limiting reagent. At the same time the excess hydrazine protects the reagent against oxidation by atmospheric oxygen through a catalytic cycle (Scheme 1b). The solvent is purged by the nitrogen evolved in the reduction and an inert atmosphere is needed only for prolonged reaction periods.

A prerequisite for the titration method is that the diselenide is rigorously purified from adhered diphenyl triselenide. Otherwise an orange-brown color persists in the reduced solution. The combination of hydrazine and base reduces selenium to highly colored polyselenide ions⁷ and an excess of selenium even at a level of 0.2 mol% (below the limit for detection by conventional analysis) prevents the observation of a defined end-point. We prepared **2** in a satisfactory quality by purification *via* dihydroxy phenylselenonium toluene-*p*-sulfonate.⁸

Compound 1 is not oxidized by DMSO. No trace of 2 is



observed after exposure of the reagent solution to 120 °C for 24 h. In contrast DMSO oxidizes the neutral benzeneselenol quantitatively into **2** within minutes at room temperature. In this way an excess of reagent is efficiently quenched upon addition of the equivalent amount of acid. On the other hand the reduction of **2** in DMSO cannot be used for reaction sequences which involve either the production of benzeneselenol or an acid catalyzed reaction of **1** as a subsequent step. Solutions of benzeneselenol can be generated when the titration procedure is carried out in *N*-methylpyrrolidone (NMP) and the equivalent amount of acid is subsequently added. 3-(Phenylseleno)propanenitrile (**3**) has been prepared from acrylonitrile and methyl 3-(phenylseleno)propanoate (**4**) from methyl acrylate by application of this modification (Scheme 2, i).

$$\begin{array}{cccc} 1 + CH_2 = CH-Z & \stackrel{i}{\longrightarrow} & PhSeCH_2CH_2 - Z \\ & 3: Z = CN \\ & 4: Z = CO_2Me \end{array}$$

$$1 + PhCO_2Me & \stackrel{ii}{\longrightarrow} & PhCO_2^- + PhSeMe \\ 1 + Ar-X & \stackrel{iii}{\longrightarrow} & Ar-SePh \\ & 5-10 & 11-16 \end{array}$$

Scheme 2 Conditions: i, NMP, 1 equiv. of AcOH, 20 °C, 15 min; ii, DMSO, 2 equiv. of 1, 95 °C, 3 h; iii, DMSO, N₂ atmosphere, temperature and reaction period: see Table 1.

The demethylation of methyl benzoate (Scheme 2, ii) was investigated in order to assess the nucleophilic reactivity of **1** in the present solvent. Liotta *et al.*⁴ reported that this reaction is completed in 3 h in refluxing THF–HMPA (5:1). With identical reagent concentrations we observed the same reaction period at 95 °C. As could be expected the reactivity of **1** is slightly lowered by hydroxylic solvation in DMSO–methanol but not more than can be compensated by the higher reaction temperatures accessible in this solvent.

The utilization of an elevated reaction temperature makes it possible to extend the range of aryl halides which can undergo uncatalyzed nucleophilic substitution with 1 (Scheme 2, iii). A series of examples indicating the conditions for and the scope of the reaction is presented in Table 1.

The conversions of halobenzonitriles, 7, and 8, into 13 and 14, respectively, have previously been effected only with Nicatalysis⁹ or by electrochemical stimulation.¹⁰ An excess of 1 was applied in the preparation of 15 in order to suppress the by-products from a competing unimolecular elimination of isobutene from 9. The relative reaction rates of 7 and 8 as well as the product distribution from 10 show that the order of reactivity is ArBr > ArCl. This feature indicates that the observed substitutions take place by a S_{RN}1 type of mechanism.¹¹ The transformation of 10 appears to represent the limit of the uncatalyzed thermal substitution reaction. Little or no product was observed from simple aryl halides or from aryl halides with a *meta*-acceptor substituent.

In conclusion the reduction of **2** with hydrazine hydrate and sodium methanolate in DMSO or NMP provides a rapid route

J. Chem. Soc., Perkin Trans. 1, 1999, 1915–1916 1915

 Table 1
 Nucleophilic aromatic substitution with 1 in DMSO–MeOH

Substrate	Product	<i>t</i> /h	<i>T/</i> °C	Yield (%)
NO ₂ Br	NO ₂ SePh	1	20	76 <i>ª</i>
5 O ₂ N 6 Br	11 D ₂ N SePh	1	20	79 <i>ª</i>
	CN SePh	1	125	72 <i>ª</i>
NC Br	NC SePh 14	20	125	68 <i>ª</i>
$\bigcup_{Br}^{CO_2Bu^t}$	CO ₂ Bu ^t SePh	20	125	48 ^a
Cl	Cl SePh	24	125	54 <i>^b</i>
Br 10	16 Br SePh	24	125	6 <i>^b</i>

^{*a*} Of isolated, pure compound. ^{*b*} Inseparable product mixture, composition analyzed by GC-MS.

to clean solutions of **1** containing a precisely defined amount of a reagent with a sufficiently high nucleophilic reactivity for most synthetic purposes.

Experimental

Preparation of 1 M sodium benzeneselenolate solutions

DMSO (Lab-Scan), 25% sodium methanolate in methanol (Aldrich) and hydrazine hydrate (Fluka) were used directly. NMP (Aldrich) was distilled from sodium methanolate prior to use in order to remove an unknown impurity causing a red coloring of the reagent solution. Diphenyl diselenide (2) was purified by oxidation to dihydroxy phenylselenonium toluene*p*-sulfonate followed by reduction of the recrystallized salt according to ref 8. To a stirred solution containing 2 (5 mmol) and hydrazine hydrate (2.75 mmol) in DMSO or NMP (8 ml) was added 25% methanolic sodium methanolate (approximately 2 g, the last 0.2 g added dropwise with intervals of 5 s until the yellow color of 2 disappeared). A reagent with increased reactivity can be obtained by removing the methanol, *e.g.* at 60 °C, 1-2 kPa (membrane pump) or at ~90 °C in a stream of nitrogen.

Conjugate addition of benzeneselenol

To a solution of **1** (10 mmol) prepared in NMP was added a mixture of acetic acid (10 mmol) and the appropriate acrylic acid derivative (10 mmol). After 10 min the mixture was poured into water and the product isolated by extraction (hexane–ethyl acetate, 4:1), flash chromatography (silica gel 60) and bulb-to-bulb distillation (10 Pa, air bath 200 °C). Yields: **3**, 93%, purity (GC-MS), 98%; **4**, 84%, purity (GC-MS), 96%.

(Phenylseleno)arenes (11–17)

The haloarene (10 mmol) was added to a solution of **1** (10 mmol) and the mixture was stirred in a nitrogen atmosphere as specified in Table 1. The reaction mixture was poured into water and extracted with ether. The ether phase was filtered through alumina (neutral, 6 g) and solid residues from evaporation were recrystallized: 2-nitrophenyl phenyl selenide (11), mp 90 °C (from ethanol) (lit.,¹² 91 °C); 4-nitrophenyl phenyl selenide (12), mp 60 °C (from ethanol) (lit.,¹² 54 °C); 2-(phenylseleno)-benzonitrile (13), mp 73 °C (from methanol) (lit.,^{10a} 70 °C); 4-(phenylseleno)benzonitrile (14), mp 52 °C (from hexane) (lit.,¹³ 52 °C). A 50% excess of **1** was applied in the preparation of tert-butyl 2-(phenylseleno)benzoate (15). The product was purified by column chromatography (silica gel 60, pentane). Colorless oil [Found: C, 61.2%; H 5.5%; M⁺ (⁸⁰Se) 334; δ (⁷⁷Se) (57.3 MHz; CDCl₃; Me₂Se), 469 ppm.

Notes and references

- R. Monahan, D. Brown, L. Waykole and D. Liotta, in *Organo-selenium Chemistry*, ed. D. Liotta, John Wiley & Sons, New York, 1987, ch. 4.
- 2 D. L. Klayman, in *Organic Selenium Compounds*, eds. D. L. Klayman and W. H. H. Günther, John Wiley & Sons, New York, 1973, p. 71, 96.
- 3 (a) B. Sjögren and S. Herdevall, Acta Chem. Scand., 1958, 12, 1347; (b) K. B. Sharpless and R. F. Lauer, J. Am. Chem. Soc., 1973, 95, 2697.
- 4 (a) D. Liotta, W. Markiewick and H. Santisteban, *Tetrahedron Lett.*, 1977, **50**, 4365; (b) D. Liotta, U. Sunay, H. Santisteban and W. Markiewick, J. Org. Chem., 1981, **46**, 2605.
- 5 P. Dowd and P. Kennedy, Synth. Commun., 1981, 11, 935.
- 6 L. Syper and J. Mlochowski, Synthesis, 1984, 439.
- 7 H. Eggert, O. Nielsen and L. Henriksen, J. Am. Chem. Soc., 1986, 108, 1725.
- 8 L. Henriksen and N. Stuhr-Hansen, Synth. Commun., 1996, 26, 1897.
- 9 H. J. Christau, B. Chabaud, R. Labaudiniere and H. Christol, Organometallics, 1985, 4, 657.
- 10 (a) C. Degrand, J. Org. Chem., 1987, 52, 1421; (b) C. Degrand, R. Prest and M. Nour, Phosphorus Sulfur, Relat. Elem., 1988, 38, 201.
- 11 A. B. Pierini and R. A. Rossi, J. Org. Chem., 1979, 44, 4667.
- 12 L. Engman and D. Stern, J. Org. Chem., 1994, 59, 5179.
- 13 C. J. Degrand, J. Chem. Soc., Chem. Commun., 1986, 1113.

Communication 9/03686E