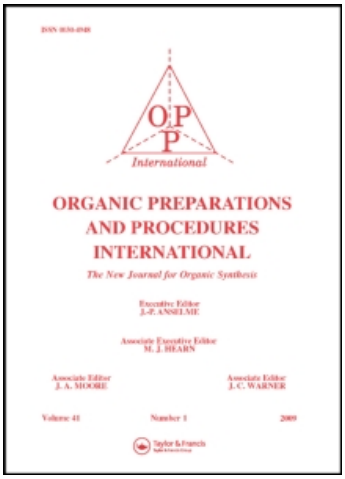

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IMPROVED SYNTHESIS OF PHENYLSELENOGLYCOLIC ACIDS

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IMPROVED SYNTHESIS OF PHENYLSELENOGLYCOLIC ACIDS

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(10/28/03)

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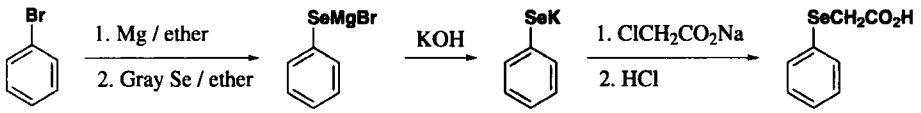
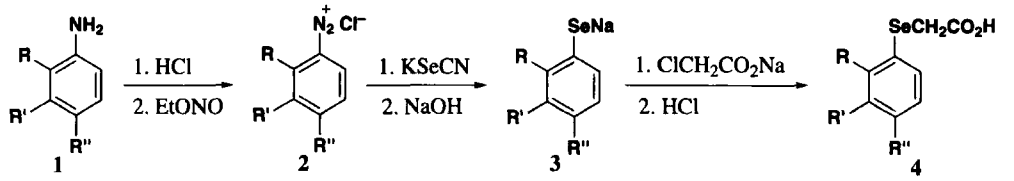
Selenium is a nonmetallic trace element recognized as a nutrient essential to human health.[1,2] Selenium is also an essential constituent of extracellular and cellular glutathione peroxidases, thyroidal and extrathyroidal iodothyronine 5'-deiodinnases, thioredoxin reductase, and other selenoproteins.[2] Various experimental models showed that selenium inhibits tumorigenesis.[3] Low serum selenium levels are associated with an increased risk of developing cancer at several sites, especially cancers of the stomach and lung for men[4]. Thus, many organoselenium compounds have been synthesized.[5,6] Some substituted phenylselenoglycolic acids have been synthesized by using Grignard reagent[7] (*Scheme 1*) (yields 20-25%) and from



Scheme 1

diazonium salts.[8,9] In the studies with diazonium salts, substituted anilines were diazotized in aqueous medium, followed by addition of potassium selenocyanide. Although yields were not reported,[8,9] we found them to be lower (25-30%) when the last traces of acids were not removed and reaction performed in aqueous medium. In the presence of acid, potassium selenocyanide decomposes to release poisonous hydrogen cyanide and concurrent decrease in the yields.

In our method (*Scheme 2*), substituted anilinium chlorides are prepared, dried and washed with ether to remove excess acid from the salts. The anilinium chlorides are diazotized with ethyl nitrite in non-aqueous medium, thus avoiding the decomposition of potassium selenocyanide.



a) R = Cl , R', R" = H; b) R, R' = H, R" = Cl; c) R = Br , R', R" = H; d) R, R' = H, R" = Br; e) R, R' = H, R" = CH_3; f) R = NO_2 , R', R"= H; g) R, R" = H , R' = NO_2; h) R, R' = H, R" = NO_2; i) R, R' = H, R" = COOH

Scheme 2

Table 1. Yields, mps ^{1}H NMR and IR Spectral Data of **4**

Cmpd	mp (°C)	*lit* mp (°C)	Yield (%)	^{1}H NMR (δ) ($CDCl_3$; CF_3COOH)	IR (cm^{-1}) O-H,	C=O,	=CH,	CH
4a	89-90	87-89[a]	34	3.70 (s, 2H) ; 7.24 (m,4H); 10 (s,1H)	3480,	1703,	3075,	2993
4b	110-113	114[b]	46	3.40 (s, 2H) ; 7.0-7.78 (m, 4H); 9.8 (s,1H)	3428,	1705,	3074,	2921
4c	90-91	92[a]	36	3.60 (s, 2H) ; 7.1-7.4 (m, 4H); 9.1 (s,1H)	3461,	1708,	3082,	2921
4d	126-127	127[c]	50	3.40 (s, 2H); 7.0 (m, 4H); 9.0 (s,1H)	3454,	1709,	3082,	2903
4e	94-95	97-98[b]	48	2.19 (s, 3H); 3,38 (s, 2H); 6.95-7.24 (m, 4H); 9.78 (s,1H)	3435,	1702,	3070,	2928
4f	160-163	165[b]	35	3.40 (s, 2H); 7-8 (m, 4H) 9.2 (s, 1H)	3461,	1715,	3024,	2921
4g	88-90	90-91[b]	40	3.90 (s, 2H); 7.40-8.11 (m, 4H)	3505,	1708,	3089,	2921
4h	117-120	119-120[b]	48	3.38 (s, 2H); 6.95-7.24 (m, 4H)	3416,	1702,	3262,	2900
4i	245-250	250[a]	45	3.20 (s, 2H); 7.0-8.0 (m, 4H); 9.1 (s,1H)	3448,	1683,	3121	2928

a) Ref 9; b) Ref 8; c) Ref 7

EXPERIMENTAL SECTION

The anilines and other chemicals were supplied by Merck Co. All mps were determined in sealed capillaries and are uncorrected. FT-IR spectra were recorded on a Matson 1000 spectrometer as KBr pellets. ^{1}H NMR spectra were obtained on a Varian EM-360 L (60 MHz) NMR spectrometer and a Varian Gemini 200 (200 MHz) NMR spectrometer in $CDCl_3$.

2-Chlorophenylselenoglycolic acid (4a). Typical Procedure.- 2-Chloroaniline (1.08 mL, 0.01 mole) and conc. HCl (2.7 mL, 0.04 mole) were mixed slowly. The anilinium chloride was collected, air-dried and dissolved in 30 mL of absolute alcohol. The stirred solution was cooled –5-0°C and diazotized by the careful dropwise addition (over a period of 30 minutes) of ethyl nitrite (1 mL, 0.006 mole). Both the solution and ethyl nitrite (its bp 17°C) must be cold (–5-0°C) during the addition. Then a solution of KSeCN (1.44 g, 0.01 mole) in 30 mL of absolute alcohol was added into the solution of the diazonium salt. The precipitate which formed was collected, air dried and dissolved in about 30 mL of boiling ethanol. Then, a solution of NaOH (0.8 g, 0.02 mole) in ethanol was added to the boiling solution and this mixture was refluxed 2 hrs. The mixture was cooled at room temperature and then 5 mL water was added. Then a solution of

sodium chloroacetate (0.01 mole, 1.165 g) in cold water was poured into the final solution and the mixture was boiled under reflux for 15 minutes. The alcohol was evaporated *in vacuo*. The cooled mixture was filtered and HCl was added the filtrate until precipitation was complete. The precipitate obtained was recrystallized from benzene (water for **4c-4i**) to afford 0.85 g (34%) of colorless needles, mp. 89-90°C, *lit.*[a] 87-89°C.

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