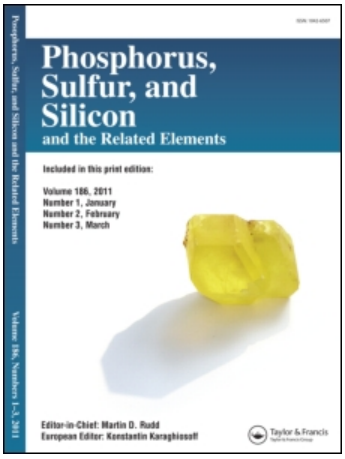

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SYNTHESIS OF HETEROCYCLES ON THE BASIS OF ARYLATION PRODUCTS OF UNSATURATED COMPOUNDS. 11.[1] 5-R-BENZYL-2-IMINOSELENAZOLIDIN-4-ONES FROM ETHYL 3-ARYL-2-BROMOPROPANOATES

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SYNTHESIS OF HETEROCYCLES ON THE BASIS OF ARYLATION PRODUCTS OF UNSATURATED COMPOUNDS. 11.[1] 5-R-BENZYL-2-IMINOSELENAZOLIDIN-4-ONES FROM ETHYL 3-ARYL-2-BROMOPROPANOATES

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Ethyl 3-aryl-2-bromopropanoates ***2a–p*** *were prepared by reaction of ethyl acrylate with arenediazonium bromides* ***1a–p*** *in the presence of CuBr (Meerwein arylation). These compounds react with selenourea to form 5-R-benzyl-2-iminoselenazolidin-4-ones* ***4a–p.*** *Compounds* ***4a–p*** *hydrolyze into the corresponding selenazolidin-2,4-diones.*

Keywords: 2-iminoselenazolidin-4-one; cyclization; Meerwein arylation; selenazole; selenazolidin-2,4-dione; selenourea

Organoselenium compounds permanently attract attention of chemists; this may be conditioned on their interesting reactivities and potential pharmaceutical significance. A special place among these compounds take selenium-containing heterocycles.

Much of the interest in synthesis of selenazole derivatives is due to their biological activities.[2–6] A convenient method to obtain the substituted selenazoles is the interaction between α-haloketones with compounds containing a selenoamide fragment—$H_2NC(Se)R$.[2,3,7–14] The interaction of these compounds with α-halogenocarboxylic acids and their derivatives to yield selenazolidin-4-ones have been studied considerably less.[15,16]

We suggest an approach to synthesis of selenazolidin-4-one derivatives through the products of Meerwein arylation of acrylates. Arenediazonium bromides **1a–p** react with ethyl acrylate in acetone in the

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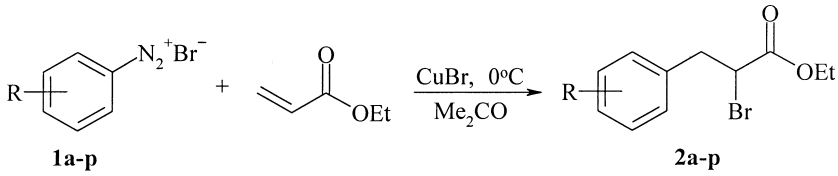
presence of CuBr yielding ethyl 3-aryl-2-bromopropanoates **2a–p** (Scheme 1). We have reported the synthesis of similar compounds earlier.[17] They are obtained in 40–60% yield.



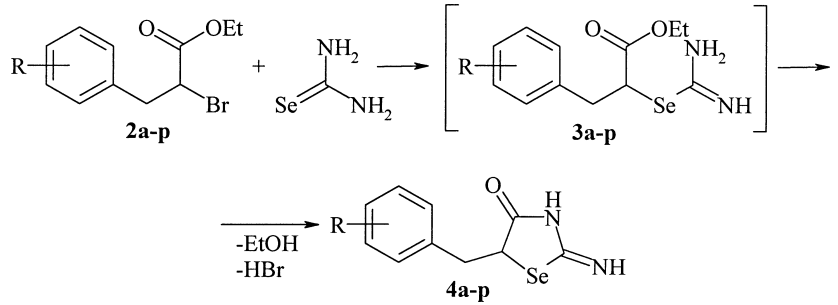
1a-p **2a-p**

2	a	b	c	d	e	f	g	h	i	j
R	H	2-Me	3-Me	4-Me	4-Et	4-Bu	4-F	2-Cl	4-Cl	4-Br

2	k	l	m	n	o	p
R	3-NO_2	4-COOEt	4-MeO	2,3-Cl_2	2,5-Cl_2	3-Cl-4-Me

SCHEME 1

It has been established that esters **2a–p** react with selenourea forming selenazole rings. Selenourea alkylated by α-bromoesters while boiling in ethanol in the presence of pyridine, affords selenouronium salts **3a–p**. Under the conditions of reaction they have cyclized to give 5-R-benzyl-2-iminoselenazolidin-4-ones **4a–p** in high yields (Scheme 2).



2a-p **3a-p** **4a-p**

SCHEME 2

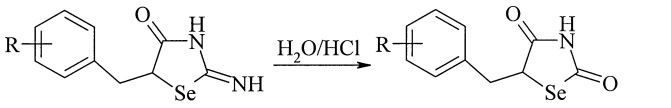
It is necessary to stress, that the compounds **2a–p** in the presence of bases can eliminate HBr forming cinnamic esters. However, under the given conditions we can escape such a reaction.

In this reaction selenourea is more efficient than thiourea:[17] reaction times are up 20–30 min and 2–3 h respectively.

Compounds of this type are characterized by imino-amino tautomerism.[16] According to ^{1}H NMR spectra in DMSO-d_6 compounds **4a–p** exist in imino form (two signals of NH groups app. ~8.5 and ~9.0 ppm).

The described method of designing a selenazolidine cycle is the first which gives the opportunity to obtain selenazole derivatives containing benzyl substituents. Besides, the availability of an amidine fragment makes it possible to utilize these compounds as a reagents in reactions of various types.

Thus, the performed research demonstrated the possibility to obtain 5-R-benzyl substituted selenazoles through the products of bromoarylation of acrylates. Selenazoles **4a–p** can be easily transformed into the corresponding selenazolidin-1,4-diones.



4g, p **5a, b**

a, R=4-F; **b**, R=3-Cl-4-Me

SCHEME 3

The prepared compounds seem to be interesting for biological activity studies. It is worth mentioning that among 5-R-benzylthiazolidin-4-ones a range of antidiabetic agents is known.[18,19]

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker 400 MHz (compounds **4c**,**e**,**i**,**k**,**m**,**p; 5a,b**) or Bruker DRX 500 MHz (compounds **4a**,**b**,**d**,**f–h**,**g**,**l**,**n**,**o**) spectrometers in DMSO-d_6. Chemical shifts are reported in ppm relative to the residual signal of the solvent. Coupling constants (J) are indicated in Hz. Mass spectra were obtained using a Finnigan MAT INKOS-50 chromatomass spectrometer at 70 eV.

General Procedure for the Synthesis of Ethyl 3-Aryl-2-bromopropanoates (2a–p)

A solution of $NaNO_2$ (16.6 g, 0.24 mmol) in H_2O (30 ml) was added dropwise to a stirred and ice-cooled mixture of the substituted aniline (0.22 mmol), aqueous HBr (47%, 95 g, 0.55 mmol), and water (30 ml)

below 0–5°C. The cold diazonium salt solution is slowly added to the vigorously stirred solution of CuBr (3 g, 21 mmol) and ethyl acrylate (22.0 g, 0.22 mmol) in acetone (150 ml) at 40°C. The reaction is exothermic and the dropping rate is adjusted at such a rate that nitrogen is evolved at 2–3 bubbles/sec (0.5–1 h). The resultant homogeneous solution is stirred for 30 min at 40°C and diluted with H_2O. The organic phase is dried with $MgSO_4$, and concentrated. The residue is purified by distillation under reduced pressure to give ethyl 3-aryl-2-bromopropanoates (40–60% yield).

General Procedure for the Synthesis of 5-R-benzyl-2-iminoselenazolidin-4-ones (4a–p)

A mixture of **2a–p** (4.1 mmol), pyridine (0.32 g, 4.1 mmol), selenourea (0.5 g, 4.1 mmol), and ethanol (15 ml) was refluxed for 20–30 min. After cooling, the crystals were collected by filtration and recrystallized from EtOH/DMF to give the title compounds.

*5-Benzyl-2-iminoselenazolidin-4-one (**4a**).* m.p. 202–203°C in 80% yield. ^{1}H NMR ppm: δ 2.95 (dd, 1H, CH_2, ^{2}J 14.0, ^{3}J 11.0), 3.64 (dd, 1H, CH_2, ^{3}J 3.7), 4.67 (dd, 1H, CH), 7.16–7.28 (m, 5H, C_6H_5), 8.53 (s, 1H, =NH), 8.92 (br. s, 1H, NH). Anal. requires for $C_{10}H_{10}N_2OSe$ (253.16) calcd./found: C, 47.44/47.29; H, 3.98/3.93; N, 11.07/11.03.

*5-(2-Methylbenzyl)-2-iminoselenazolidin-4-one (**4b**).* m.p. 208–210°C in 66% yield. ^{1}H NMR ppm: δ 2.38 (s, 3H, CH_3), 2.93 (dd, 1H, CH_2, ^{2}J 14.7, ^{3}J 11.6), 3.72 (dd, 1H, CH_2, ^{3}J 3.7), 4.65 (dd, 1H, CH), 7.06–7.17 (m, 4H, C_6H_4), 8.55 (s, 1H, =NH), 8.95 (br. s, 1H, NH). Anal. requires for $C_{11}H_{12}N_2OSe$ (267.19) calcd./found: C, 49.45/49.38; H, 4.53/4.45; N, 10.48/10.59.

*5-(3-Methylbenzyl)-2-iminoselenazolidin-4-one (**4c**).* m.p. 181–182°C in 75% yield. ^{1}H NMR ppm: δ 2.31 (s, 3H, CH_3), 2.87 (dd, 1H, CH_2, ^{2}J 14.0, ^{3}J 11.2), 3.58 (dd, 1H, CH_2, ^{3}J 3.6), 4.70 (dd, 1H, CH), 6.98–7.04 (m, 3H, C_6H_4), 7.15 (t, 1H, C_6H_4), 8.71 (s, 1H, =NH), 9.08 (br. s, NH; exchangeable). Anal. requires for $C_{11}H_{12}N_2OSe$ (267.19) calcd./found: C, 49.45/49.57; H, 4.53/4.51; N, 10.48/10.40.

*5-(4-Methylbenzyl)-2-iminoselenazolidin-4-one (**4d**).* m.p. 207°C in 73% yield. ^{1}H NMR ppm: δ 2.31 (s, 3H, CH_3), 2.91 (dd, 1H, CH_2, ^{2}J 14.1, ^{3}J 10.8), 3.60 (dd, 1H, CH_2, ^{3}J 3.9), 4.64 (dd, 1H, CH), 7.05 (d, 2H, C_6H_4, ^{3}J 7.2), 7.10 (d, 2H, C_6H_4), 8.52 (s, 1H, =NH), 8.90 (br. s, 1H, NH). Anal. requires for $C_{11}H_{12}N_2OSe$ (267.19) calcd./found: C, 49.45/49.31; H, 4.53/4.49; N, 10.48/10.45.

*5-(4-Ethylbenzyl)-2-iminoselenazolidin-4-one (**4e**).* m.p. 184–185°C in 75% yield. ^{1}H NMR ppm: δ 1.21 (t, 3H, CH_3), 2.59 (q, 2H, CH_2), 2.89 (dd, 1H, CH_2, ^{2}J 14.4, ^{3}J 10.8), 3.57 (dd, 1H, CH_2, ^{3}J 4.0), 4.70 (dd,

1H, CH), 7.09 (d, 2H, C_6H_4, ^3J 8.4), 7.12 (d, 2H, C_6H_4), 8.77 (br. s, NH; exchangeable). Anal. requires for $C_{12}H_{14}N_2OSe$ (281.21) calcd./found: C, 51.25/51.18; H, 5.02/4.91; N, 9.96/9.89.

*5-(4-Butylbenzyl)-2-iminoselenazolidin-4-one (**4f**)*. m.p. 195°C in 80% yield. ^{1}H NMR ppm: δ 0.94 (t, 3H, CH_3), 1.36 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 2.56 (t, 2H, CH_2), 2.90 (dd, 1H, CH_2, ^2J 14.0, ^3J 10.8), 3.62 (dd, 1H, CH_2, ^3J 3.7), 4.63 (dd, 1H, CH), 7.05 (d, 2H, C_6H_4, ^3J 7.9), 7.11 (d, 2H, C_6H_4, ^3J 7.9), 8.54 (s, 1H, =NH), 8.95 (br. s, 1H, NH). Anal. requires for $C_{14}H_{18}N_2OSe$ (309.27) calcd./found: C, 54.37/54.23; H, 5.87/5.82; N, 9.06/9.11.

*5-(4-Fluorobenzyl)-2-iminoselenazolidin-4-one (**4g**)*. m.p. 189–191°C in 78% yield. ^{1}H NMR ppm: δ 3.00 (dd, 1H, CH_2, ^2J 14.4, ^3J 7.6), 3.58 (dd, 1H, CH_2, ^3J 4.4), 4.68 (dd, 1H, CH), 7.03–7.09 (m, 2H, C_6H_4), 7.24–7.29 (m, 2H, C_6H_4), 8.63 (br. s, NH; exchangeable). Anal. requires for $C_{10}H_9FN_2OSe$ (271.15) calcd./found: C, 44.30/44.20; H, 3.35/3.27; N, 10.33/10.24.

*5-(2-Chlorobenzyl)-2-iminoselenazolidin-4-one (**4h**)*. m.p. 193–194°C in 83% yield. ^{1}H NMR ppm: δ 3.07 (dd, 1H, CH_2, ^2J 14.4, ^3J 10.5), 3.80 (dd, 1H, CH_2, ^3J 3.6), 4.78 (dd, 1H, CH), 7.18–7.26 (m, 2H, C_6H_4), 7.31 (d, 1H, C_6H_4), 7.35 (d, 1H, C_6H_4), 8.60 (s, 1H, =NH), 9.02 (br. s, 1H, NH). Anal. requires for $C_{10}H_9ClN_2OSe$ (287.60) calcd./found: C, 41.76/41.84; H, 3.15/3.20; N, 9.74/9.63.

*5-(4-Chlorobenzyl)-2-iminoselenazolidin-4-one (**4i**)*. m.p. 208–209°C in 74% yield. ^{1}H NMR ppm: δ 2.98 (dd, 1H, CH_2, ^2J 14.4, ^3J 10.0), 3.54 (dd, 1H, CH_2, ^3J 4.4), 4.74 (dd, 1H, CH), 7.23 (d, 2H, C_6H_4, ^3J 8.0), 7.28 (d, 2H, C_6H_4), 8.69 (s, 1H, =NH), 9.07 (br. s, 1H, NH). Anal. requires for $C_{10}H_9ClN_2OSe$ (287.60) calcd./found: C, 41.76/41.63; H, 3.15/3.07; N, 9.74/9.71.

*5-(4-Bromobenzyl)-2-iminoselenazolidin-4-one (**4j**)*. m.p. 196–198°C in 78% yield. ^{1}H NMR ppm: δ 2.99 (dd, 1H, CH_2, ^2J 14.3, ^3J 10.4), 3.56 (dd, 1H, CH_2, ^3J 3.7), 4.67 (dd, 1H, CH), 7.17 (d, 2H, C_6H_4), 7.40 (d, 2H, C_6H_4), 8.60 (s, 1H, =NH), 8.95 (br. s, 1H, NH). Mass: (70 eV) *m/z* (%): 334 ($M^+ + 2$, 18), 332 (M^+, 24), 330 (11), 211 (39), 209 (40), 183 (54), 182 (30), 181 (28), 180 (18), 179 (12), 171 (100), 169 (98), 103 (25), 102 (48), 101 (10), 91 (22), 90 (40), 89 (32), 80 (11). Anal. requires for $C_{10}H_9BrN_2OSe$ (332.06) calcd./found: C, 36.17/36.09; H, 2.73/2.79; N, 8.44/8.55.

*5-(3-Nitrobenzyl)-2-iminoselenazolidin-4-one (**4k**)*. m.p. 205–206°C in 84% yield. ^{1}H NMR ppm: δ 3.22 (dd, 1H, CH_2, ^2J 14.4, ^3J 8.8), 3.62 (dd, 1H, CH_2, ^3J 4.4), 4.85 (dd, 1H, CH), 7.57 (t, 1H, C_6H_4), 7.68 (d, 1H, C_6H_4, ^3J 7.6), 8.08 (d, 1H, C_6H_4, ^3J 8.0), 8.10 (s, 1H, C_6H_4), 8.70 (s, 1H, =NH), 9.08 (br. s, 1H, NH). Anal. requires for $C_{10}H_9N_3O_3Se$ (298.16) calcd./found: C, 40.28/40.04; H, 3.04/3.01; N, 14.09/14.12.

*5-(4-Ethyloxycarbonylbenzyl)-2-iminoselenazolidin-4-one (**4l**)*. m.p. 197–198°C in 65% yield. ^{1}H NMR ppm: δ 1.38 (t, 3H, CH_3), 3.08 (dd, 1H, CH_2, ^{2}J 14.0, ^{3}J 10.4), 3.68 (dd, 1H, CH_2, ^{3}J 3.7), 4.32 (q, 2H, CH_2), 4.73 (dd, 1H, CH), 7.34 (d, 2H, C_6H_4, ^{3}J 7.9), 7.90 (d, 2H, C_6H_4, ^{3}J 8.5), 8.70 (br. s, NH; exchangeable). Anal. requires for $C_{13}H_{14}N_2O_3Se$ (325.22) calcd./found: C, 48.01/47.94; H, 4.34/4.27; N, 8.61/8.50.

*5-(4-Methoxybenzyl)-2-iminoselenazolidin-4-one (**4m**)*. m.p. 188–189°C in 68% yield. ^{1}H NMR ppm: δ 2.88 (dd, 1H, CH_2, ^{2}J 14.0, ^{3}J 10.8), 3.51 (dd, 1H, CH_2, ^{3}J 4.0), 3.74 (s, 3H, CH_3), 4.70 (dd, 1H, CH), 6.80 (d, 2H, C_6H_4, ^{3}J 8.4), 7.12 (d, 2H, C_6H_4), 8.67 (s, 1H, =NH), 9.03 (br. s, 1H, NH). Anal. requires for $C_{11}H_{12}N_2O_2Se$ (283.19) calcd./found: C, 46.66/46.49; H, 4.27/4.22; N, 9.89/9.99.

*5-(2,3-Dichlorobenzyl)-2-iminoselenazolidin-4-one (**4n**)*. m.p. 204–206°C in 67% yield. ^{1}H NMR ppm: δ 3.15 (dd, 1H, CH_2, ^{2}J 14.0, ^{3}J 10.4), 3.83 (dd, 1H, CH_2, ^{3}J 4.3), 4.76 (dd, 1H, CH), 7.23 (t, 1H, C_6H_3), 7.28 (d, 1H, C_6H_3, ^{3}J 7.3), 7.41 (d, 1H, C_6H_3, ^{3}J 7.9), 8.63 (s, 1H, =NH), 9.03 (br. s, 1H, NH). Mass: (70 eV) *m/z* (%): 324 (M^++2, 1.3), 322 (M^+, 2), 320 (0.8), 289 (24), 287 (58), 285 (28), 219 (40), 217 (100), 215 (49), 182 (28), 161 (35), 159 (57), 136 (21), 102 (21), 89 (25), 75 (25). Anal. requires for $C_{10}H_8Cl_2N_2OSe$ (322.05) calcd./found: C, 37.30/37.29; H, 2.50/2.50; N, 8.70/8.70.

*5-(2,5-Dichlorobenzyl)-2-iminoselenazolidin-4-one (**4o**)*. m.p. 217–218°C in 72% yield. ^{1}H NMR ppm: δ 3.10 (dd, 1H, CH_2, ^{2}J 14.7, ^{3}J 10.4), 3.75 (dd, 1H, CH_2, ^{3}J 4.3), 4.76 (m, 1H, CH), 7.23 (dd, 1H, C_6H_3, ^{3}J 8.6, ^{4}J 1.2), 7.33–7.37 (m, 2H, C_6H_3), 8.59 (s, 1H, =NH), 9.00 (br. s, 1H, NH). Anal. requires for $C_{10}H_8Cl_2N_2OSe$ (322.05) calcd./found: C, 37.30/37.18; H, 2.50/2.42; N, 8.70/8.82.

*5-(3-Chloro-4-methylbenzyl)-2-iminoselenazolidin-4-one (**4p**)*. m.p. 196°C in 70% yield. ^{1}H NMR ppm: δ 2.31 (s, 3H, CH_3), 2.95 (dd, 1H, CH_2, ^{2}J 14.0, ^{3}J 10.0), 3.51 (dd, 1H, CH_2, ^{3}J 4.0), 4.74 (dd, 1H, CH), 7.07 (dd, 1H, C_6H_3, ^{3}J 8.0, ^{4}J 1.4), 7.20 (d, 1H, C_6H_3, ^{3}J 8.0), 7.23 (d, 1H, C_6H_3, ^{4}J 1.4), 8.73 (s, 1H, =NH), 9.10 (br. s, NH; exchangeable). Anal. requires for $C_{11}H_{11}ClN_2OSe$ (301.64) calcd./found: C, 43.80/43.71; H, 3.68/3.58; N, 9.29/9.33.

General Procedure for the Synthesis of 5-R-benzylselenazolidin-1,4-diones (5a,b)

A mixture of 5-R-benzyl-2-iminoselenazolidin-4-one (6.0 mmol) in concentrated hydrochloric acid (15 ml) was refluxed for 3 h and cooled. The crystals were collected by filtration, washed several times with water, and recrystallized from EtOH/DMF to give the title compounds.

*5-(4-Fluorobenzyl)selenazolidin-1,4-dione (**5a**)*. m.p. 209–211°C in 42% yield. ^{1}H NMR ppm: δ 3.23 (dd, 1H, CH_2, ^{2}J 14.4, ^{3}J 7.6), 3.50 (dd, 1H, CH_2, ^{3}J 4.4), 4.91 (dd, 1H, CH), 7.02–7.09 (m, 2H, C_6H_4), 7.23–7.30 (m, 2H, C_6H_4), 11.27 (br. s, NH; exchangeable). Anal. requires for $C_{10}H_8FNO_2Se$ (272.14) calcd./found: C, 44.14/43.90; H, 2.96/2.88; N, 5.15/5.19.

*5-(3-Chloro-4-methylbenzyl)selenazolidin-1,4-dione (**5b**)*. m.p. 202–203°C in 38% yield. ^{1}H NMR ppm: δ 2.31 (s, 3H, CH_3), 3.20 (dd, 1H, CH_2, ^{2}J 14.4, ^{3}J 7.6), 3.47 (dd, 1H, CH_2, ^{3}J 4.8), 4.92 (dd, 1H, CH), 7.09 (d, 1H, C_6H_3, ^{3}J 7.6), 7.23 (d, 1H, C_6H_3), 7.27 (s, 1H, C_6H_3), 11.28 (br. s, NH; exchangeable). Anal. requires for $C_{11}H_{10}ClNO_2Se$ (302.62) calcd./found: C, 43.66/43.59; H, 3.33/3.40; N, 4.63/4.56.

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