Unusual multi-component condensation in the synthesis of 1,4-dihydro-1,6-naphthyridine derivatives

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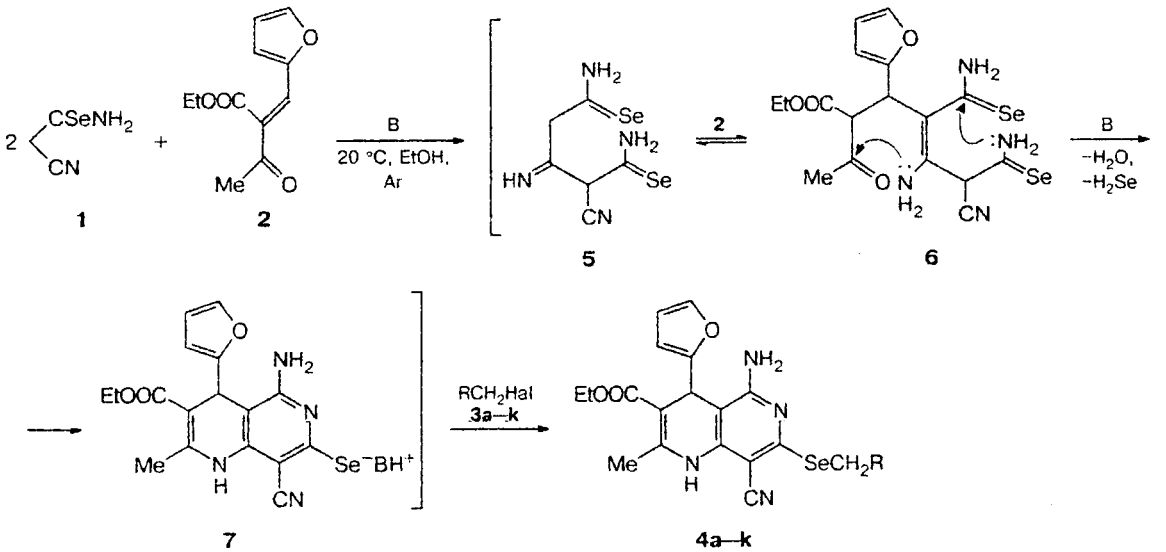
Multi-component condensation of cyanoselenoacetamide with ethyl 2-furfurylidenacetoacetate and liquid alkyl halides, catalyzed by *N*-methylmorpholine, affords 7-alkylseleno-5-amino-8-cyano-3-ethoxycarbonyl-4-(2-furyl)-2-methyl-1,4-dihydro-1,6-naphthyridines, which have not been described hitherto.

Key words: multi-component condensation, cyanoselenoacetamide, ethyl 2-furfurylidenacetoacetate, alkyl halides, *N*-methylmorpholine, 1,6-naphthyridine.

Recently, the first report concerning the synthesis of substituted alkylseleno-1,6-naphthyridine from acyclic precursors has been published.[1] While developing studies aimed at searching for new biologically active compounds in the series of 1,6-naphthyridines, we found that multi-component condensation of cyanoselenoacetamide (**1**) with ethyl 2-furfurylidenacetoacetate (**2**) and liquid alkyl halides **3a—k** (Scheme 1) in the presence of a twofold excess of *N*-methylmorpholine in anhydrous ethanol in an atmosphere of argon at 20 °C yields previously unknown 1,4-dihydro-1,6-naphthyridine derivatives **4a—k**, which are likely to be biologically active.[2—5] It is interesting that the use of solid alkyl halides instead of liquid ones affords substituted

Scheme 1



B — *N*-methylmorpholine

4	a	b	c	d	e	f	g	h	i	j	k
R	H	Me	Et	Pr^n	C_5H_{11}	CH_2Br	$(CH_2)_3Br$	C(Me)=CH_2	C≡CH	Ph	COOEt
Hal	I	I	Br	I	Br	Br	Br	Cl	Br	Cl	Cl

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Table 1. Main characteristics of compounds **4a—k**

Compound	Yield (%)	M.p./°C (solvent for crystallization)	Found / Calculated (%) C	H	N	Se	Molecular formula
4a	39	226—228 (EtOH)	51.62 / 51.80	4.48 / 4.35	13.51 / 13.43	18.96 / 18.92	$C_{18}H_{18}N_4O_3Se$
4b	36	234—235 (EtOH)	52.67 / 52.90	4.81 / 4.67	13.08 / 12.99	18.15 / 18.31	$C_{19}H_{20}N_4O_3Se$
4c	41	214—215 (EtOH)	53.78 / 53.93	5.09 / 4.98	12.67 / 12.58	17.82 / 17.73	$C_{20}H_{22}N_4O_3Se$
4d	43	158—159 (EtOH)	55.01 / 54.90	5.06 / 5.27	12.38 / 12.19	17.02 / 17.19	$C_{21}H_{24}N_4O_3Se$
4e	52	172—173 (EtOH)	56.43 / 56.67	5.94 / 5.79	11.54 / 11.49	16.07 / 16.20	$C_{23}H_{28}N_4O_3Se$
4f	34	237—239, decomp. (BuOH)	44.51 / 44.72	3.96 / 3.75	11.13 / 10.98	15.60 / 15.48	$C_{19}H_{19}BrN_4O_3Se$
4g	42	248—250 (BuOH—DMF, 4 : 1)	46.61 / 46.85	4.57 / 4.31	10.49 / 10.41	14.49 / 14.67	$C_{21}H_{23}BrN_4O_3Se$
4h	31	184—186 (MeOH)	55.31 / 55.14	4.67 / 4.85	12.59 / 12.25	17.04 / 17.26	$C_{21}H_{22}N_4O_3Se$
4i	35	195—197, decomp. (MeOH)	54.52 / 54.43	3.92 / 4.11	12.85 / 12.69	17.68 / 17.89	$C_{20}H_{18}N_4O_3Se$
4j	54	184—186 (MeOH)	58.51 / 58.42	4.52 / 4.49	11.18 / 11.36	15.94 / 16.00	$C_{24}H_{22}N_4O_3Se$
4k	29	157—159 (MeOH)	51.39 / 51.54	4.47 / 4.53	11.58 / 11.45	16.04 / 16.13	$C_{21}H_{22}N_4O_5Se$

Table 2. Spectral characteristics of compounds **4a—k**

Compound	IR, ν/cm^{-1}: NH, NH_2	δ NH_2, CO	CN	^{1}H NMR, δ (*J*/Hz)
4a	3283, 3314, 3378	1643, 1682	2208	1.21 (t, 3 H, CH_3CH_2O, *J* = 6.5); 2.38 (s, 6 H, $SeCH_3$, C(2)Me)*; 4.07 (q, 2 H, CH_3CH_2O, *J* = 6.5); 5.13 (s, 1 H, C(4)H); 6.14 (d, 1 H, C(3)H furyl, *J* = 3.0); 6.27 (dd, 1 H, C(4)H furyl, *J* = 3.0, 2.2); 6.91 (br.s, 2 H, NH_2); 7.40 (d, 1 H, C(5)H furyl, *J* = 2.2); 8.79 (s, 1 H, NH)
4b	3241, 3278, 3313, 3369	1637, 1713	2197	1.22 (t, 3 H, CH_3CH_2O, *J* = 6.5); 1.41 (t, 3 H, Me, *J* = 7.0); 2.38 (s, 3 H, C(2)Me); 3.12 (q, 2 H, $SeCH_2$, *J* = 7.4); 4.06 (q, 2 H, CH_3CH_2O, *J* = 6.1); 5.13 (s, 1 H, C(4)H); 6.15 (d, 1 H, C(3)H furyl, *J* = 3.1); 6.26 (dd, 1 H, C(4)H furyl, *J* = 3.1, 2.2); 6.89 (br.s, 2 H, NH_2); 7.40 (d, 1 H, C(5)H furyl, *J* = 2.2); 8.76 (s, 1 H, NH)
4c	3263, 3350, 3392	1627, 1691	2204	0.96 (t, 3 H, Me, *J* = 6.8); 1.21 (t, 3 H, CH_3CH_2O, *J* = 7.2); 1.69 (q, 2 H, CH_2, *J* = 7.7); 2.38 (s, 3 H, C(2)Me); 3.15 (t, 2 H, $SeCH_2$, *J* = 6.8); 4.07 (q, 2 H, CH_3CH_2O, *J* = 7.0); 5.13 (s, 1 H, C(4)H); 6.14 (d, 1 H, C(3)H furyl, *J* = 3.0); 6.27 (dd, 1 H, C(4)H furyl, *J* = 3.0, 2.2); 6.89 (br.s, 2 H, NH_2); 7.39 (d, 1 H, C(5)H furyl, *J* = 2.2); 8.76 (s, 1 H, NH)
4d	3290, 3315, 3407	1620, 1678	2215	0.89 (t, 3 H, Me, *J* = 6.7); 1.21 (t, 3 H, CH_3CH_2O, *J* = 6.7); 1.32—1.77 (m, 4 H, $(CH_2)_2$); 2.38 (s, 3 H, C(2)Me); 3.16 (t, 2 H, $SeCH_2$, *J* = 6.9); 4.07 (q, 2 H, CH_3CH_2O, *J* = 6.9); 5.13 (s, 1 H, C(4)H); 6.15 (d, 1 H, C(3)H furyl, *J* = 3.0); 6.26 (dd, 1 H, C(4)H furyl, *J* = 3.0, 2.2); 6.88 (br.s, 2 H, NH_2); 7.40 (d, 1 H, C(5)H furyl, *J* = 2.2); 8.76 (s, 1 H, NH)
4e	3298, 3401	1637, 1726	2207	0.85 (t, 3 H, Me, *J* = 5.1); 1.21 (t, 3 H, CH_3CH_2O, *J* = 7.2); 1.39—1.93 (m, 8 H, $(CH_2)_4$); 2.37 (s, 3 H, C(2)Me); 3.16 (t, 2 H, $SeCH_2$, *J* = 7.2); 4.07 (q, 2 H, CH_3CH_2O, *J* = 7.4); 5.13 (s, 1 H, C(4)H); 6.14 (d, 1 H, C(3)H furyl, *J* = 3.0); 6.26 (dd, 1 H, C(4)H furyl, *J* = 3.0, 2.1); 6.97 (br.s, 2 H, NH_2); 7.39 (d, 1 H, C(5)H furyl, *J* = 2.1); 8.75 (s, 1 H, NH)

(to be continued)

Table 2. (*continued*)

Compound	IR, ν/cm^{-1}				^{1}H NMR, δ (*J*/Hz)
	NH, NH_2	δ NH_2, CO		CN	
4f	3264, 3338, 3372	1620, 1708		2200	1.21 (t, 3 H, $C\underline{H}_3CH_2O$, *J* = 7.3); 2.38 (s, 3 H, C(2)Me); 2.53 (t, 2 H, CH_2Br, *J* = 5.5); 3.50 (br.s, 2 H, $SeCH_2$); 4.09 (q, 2 H, $CH_3C\underline{H}_2O$, *J* = 6.4); 5.13 (s, 1 H, C(4)H); 6.13 (d, 1 H, C(3)H furyl, *J* = 2.9); 6.27 (dd, 1 H, C(4)H furyl, *J* = 2.9, 2.0); 6.84 (br.s, 2 H, NH_2); 7.39 (d, 1 H, C(5)H furyl, *J* = 2.0); 8.68 (s, 1 H, NH)
4g	3232, 3305, 3318, 3384	1627, 1664		2198	1.21 (t, 3 H, $C\underline{H}_3CH_2O$, *J* = 7.3); 1.67—1.90 (m, 4 H, $(CH_2)_2$); 2.37 (s, 3 H, C(2)Me); 2.53 (t, 2 H, CH_2Br, *J* = 3.4); 3.20 (br.s, 2 H, $SeCH_2$); 4.08 (q, 2 H, $CH_3C\underline{H}_2O$, *J* = 7.8); 5.13 (s, 1 H, C(4)H); 6.13 (d, 1 H, C(3)H furyl, *J* = 3.0); 6.26 (dd, 1 H, C(4)H furyl, *J* = 3.0, 2.2); 6.89 (br.s, 2 H, NH_2); 7.40 (d, 1 H, C(5)H furyl, *J* = 2.2); 8.76 (s, 1 H, NH)
4h	3276, 3355, 3385	1615, 1695		2205	1.22 (t, 3 H, $C\underline{H}_3CH_2O$, *J* = 7.2); 1.77 (s, 3 H, C(Me)=); 2.38 (s, 3 H, C(2)Me); 3.91 (s, 2 H, $SeCH_2$); 4.07 (q, 2 H, $CH_3C\underline{H}_2O$, *J* = 6.8); 4.77, 5.05 (both s, each 1 H, $=CH_2$); 5.13 (s, 1 H, C(4)H); 6.14 (d, 1 H, C(3)H furyl, *J* = 3.0); 6.25 (dd, 1 H, C(4)H furyl, *J* = 3.0, 2.1); 6.95 (br.s, 2 H, NH_2); 7.40 (d, 1 H, C(5)H furyl, *J* = 2.1); 8.79 (s, 1 H, NH)
4i	3256, 3324, 3383	1625, 1673		2204	1.23 (t, 3 H, $C\underline{H}_3CH_2O$, *J* = 6.5); 2.38 (s, 3 H, C(2)Me); 3.07 (s, 1 H, ≡CH); 3.95 (d, 2 H, $SeCH_2$, *J* = 2.8); 4.10 (q, 2 H, $CH_3C\underline{H}_2O$, *J* = 5.6); 5.15 (s, 1 H, C(4)H); 6.14 (d, 1 H, C(3)H furyl, *J* = 2.9); 6.27 (dd, 1 H, C(4)H furyl, *J* = 2.9, 2.1); 6.91 (br.s, 2 H, NH_2); 7.39 (d, 1 H, C(5)H furyl, *J* = 2.1); 8.76 (br.s, 1 H, NH)
4j	3268, 3370, 3394	1635, 1720		2215	1.22 (t, 3 H, $C\underline{H}_3CH_2O$, *J* = 7.5); 2.38 (s, 3 H, C(2)Me); 4.08 (q, 2 H, $CH_3C\underline{H}_2O$, *J* = 7.9); 4.45 (s, 2 H, $SeCH_2$); 5.16 (s, 1 H, C(4)H); 6.16 (d, 1 H, C(3)H furyl, *J* = 3.2); 6.28 (dd, 1 H, C(4)H furyl, *J* = 3.2, 2.2); 7.07 (br.s, 2 H, NH_2); 7.13—7.52 (m, 6 H, C(5)H furyl, C_6H_5)*; 8.83 (s, 1 H, NH)
4k	3285, 3375	1628, 1716, 1745		2195	1.16, 1.21 (both t, each 3 H, 2 $C\underline{H}_3CH_2O$, *J* = 6.2); 2.38 (s, 3 H, C(2)Me); 4.04 (q, 2 H, $SeCH_2$, 2 $CH_3C\underline{H}_2O$, *J* = 7.9)*; 5.14 (s, 1 H, C(4)H); 6.13 (d, 1 H, C(3)H furyl, *J* = 3.2); 6.25 (dd, 1 H, C(4)H furyl, *J* = 3.2, 2.3); 6.94 (br.s, 2 H, NH_2); 7.39 (d, 1 H, C(5)H furyl, *J* = 2.3); 8.86 (s, 1 H, NH)

* Proton signals overlap.

2-alkylseleno-1,4-dihydropyridines rather than the expected 1,6-naphthyridines of type **4**, which will be reported by us elsewhere. Apparently, this is caused by the fact that the alkyl halide is accessible for reaction (because of its solubility in the reaction medium) or that halogen in this alkylating agent is relatively reactive.

A plausible mechanism of formation of naphthyridines **4a—k** is shown in Scheme 1. In the first stage, Thorpe dimerization of cyanoselenoacetamide (**1**) seems to occur to give compound **5**. Note that **1** dimerizes easily enough in such a way.[6,7] Compound **5** undergoes Michael addition to ethyl 2-furfurylidenacetoacetate (**2**) to give the corresponding adduct **6**. Under the reaction conditions, adduct **6** undergoes regioselective cyclocondensation into substituted 1,4-dihydro-1,6-naphthyridine-7-selenolate (**7**), whose further alkylation with halides **3a—k** yields selenides **4a—k**.

The unique aspect of the synthetic method proposed is that the naphthyridine system is constructed during the reaction from acyclic fragments of the starting reagents under mild conditions.

The structures of the compounds synthesized were confirmed by data of elemental analysis (Table 1) and ^{1}H NMR and IR spectroscopy (Table 2).

Experimental

Melting points were determined on a Kofler stage. IR spectra of the compounds synthesized were recorded on an IKS-29 instrument (Vaseline oil). ^{1}H NMR spectra were recorded on Bruker WP-100 SY (100 MHz) and Bruker WP-250 (250 MHz) instruments in DMSO-d_6 with Me_4Si as the internal standard.

The course of the reactions was monitored and the purity of products was checked by TLC on Silufol UV-254 plates (acetone—heptane (3 : 5), visualization with iodine vapor).

7-Alkylseleno-5-amino-8-cyano-3-ethoxycarbonyl-4-(2-furyl)-2-methyl-1,4-dihydro-1,6-naphthyridines (4a—j) (general procedure). Cyanoselenoacetamide (**1**) (1.47 g, 10 mmol) and *N*-methylmorpholine (1.05 mL, 10 mmol) were successively added with stirring to a solution of ester **2** (1.04 g, 5 mmol) in 20 mL of anhydrous ethanol in an atmosphere of argon at 20 °C. The reaction mixture was stirred for 10 min and filtered under argon through a folded filter to isolate undissolved admixtures. Then, the corresponding alkyl halide **3a—j** (5 mmol) was added. After 48—72 h, the precipitate that formed was separated and washed with ethanol.

5-Amino-8-cyano-3-ethoxycarbonyl-7-ethoxycarbonylmethylseleno-4-(2-furyl)-2-methyl-1,4-dihydro-1,6-naphthyridine (4k) was obtained analogously to compounds **4a—j**. After 72 h, the reaction mixture was diluted by water with stirring. The resin that formed was separated by decanting.

washed with water, and dissolved in ethanol. The undissolved residue was filtered off and washed with a small amount of ethanol.

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