Chemistry of Heterocyclic Compounds, Vol. 33, No. 10, 1997

SINGLE STAGE SYNTHESIS OF 2-ALKYLTHIO(SELENO)-4-HETARYL-3-CYANO-5,6,7,8-TETRAHYDROQUINOLINES

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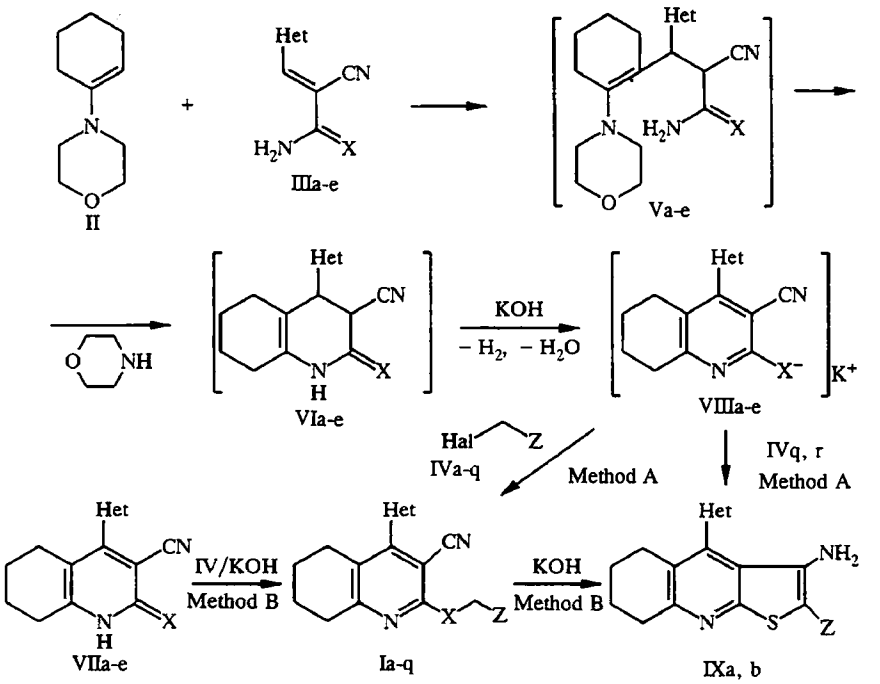
Reaction of N-(1-cyclohexenyl)morpholine, hetarylmethylenecyanothio(seleno)acetamides, and alkyl halides gives 2-alkylthio(seleno)-4-hetaryl-3-cyano-5,6,7,8-tetrahydrothieno[2,3-b]quinolines.

Derivatives of 3-cyano-5,6,7,8-tetrahydroquinolinethiones are known as biologically active materials showing, in particular, antimicrobial [1] and fungicidal [2] properties. The basic methods for their preparation include reaction of quinolin-2-ones with P_2S_5 [3, 4], reaction of 2-chloro-3-cyanoquinolines with thiourea [5], recyclization of substituted 1,3-dithia-4-



I, IVa,c-q X = S, b X = Se; *a* Hal = Br, Z = COC_6H_4Br-3, Het = 2-furyl; b Hal = I, Z = H, Het = 2-furyl; c Hal = Br, Z = 2-thenoyl, Het = 2-furylphenyl-5; d Hal = Cl, Z = COOH, Het = 2-thienyl; e Hal = Br, Z = $C_6H_4CH_3$-2, Het = 2-thienyl; f Hal = Br, Z = 2-thenoyl, Het = 2-thienyl; g Hal = Br, Z = COPh, Het = 2-thienyl; h Hal = Cl, Z = $COOCH_3$, Het = 2-thienyl; i Hal = Cl, Z = Ph, Het = 2-thienyl; j Hal = Br, Z = 3-coumarinocarbonyl, Het = 2-thienyl; k Hal = Cl, Z = $CONH_2$, Het = 2-thienyl; *l* Hal = Cl, Z = $COOCH_3$, Het = 4-pyridinyl; m Hal = Cl, Z = $CONH_2$, Het = 4-pyridinyl; n Hal = Br, Z = COC_6H_4Cl-4, Het = 4-pyridinyl; o Hal = Br, Z = 2-thenoyl, Het = 4-pyridinyl; p Hal = Br, Z = $C_6H_4CH_3$-2; Het = 4-pyridinyl; q Hal = Br, Z = COC_6H_4Cl-4, Het = 2-furylphenyl-5; r Hal = Br, Z = $COC_6H_4CH_3$-4; III, VII *a* Het = 2-furyl, X = S; b Het = 4-pyridinyl, X = S; c Het = 2-thienyl, X = S; d Het = 2-furyl, X = Se; e Het = 5-phenyl-2-furyl, X = S; IX a Z = COC_6H_4Cl-4, Het = 2-furylphenyl-5; b Z = $COC_6H_4CH_3$-4, Het = 2-thienyl

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0009-3122/97/3310-1203$18.00

cyclohexenes [6-8], reaction of arylmethylenecyclohexanones and cyanothioacetamide [1, 9], or reaction of cyclohexanone [4, 10] or its enamine [10, 11] with arylmethylenecyanothioacetamides. The corresponding substituted quinolineselenones are unknown.

We have developed a simple method for the synthesis of 2-alkylthio(seleno)-4-hetaryl-3-cyano-5,6,7,8-tetrahydroquinolines (I) by reacting N-(1-cyclohexenyl)-morpholine (II), hetarylmethylenecyanothio(seleno)acetamides (III), and alkyl halides (IV) in absolute ethanol at 20°C. The reaction apparently occurs via a Michael type addition to form the adduct (V) which then cyclizes to the hexahydroquinolin-2(1H)-chalcogenone (VI). The proposed reaction course agrees with literature data concerning the increased reactivity of enamines as nucleophiles when compared with their carbonyl analogs [12-14]. Subsequent, consecutive additions of an equimolar amount of KOH and alkyl halide IV to the reaction mixture gives quantitative yields of the chalcogenides I (method A), which were also prepared by a counter synthesis from the known [10, 11] tetrahydroquinoline-2-(1H)-chalcogenones (VII) and compound IV in the presence of base (method B). It was also found that formation of chalcogenides was not observed without addition of KOH using method A, and this can be explained by the absence of morpholine type salts VIII in the reaction mixture. Besides forming salts VIII, KOH evidently catalyzes the dehydration of the hypothetical products VI to their aromatic analogs VIII. The scheme described above (method A) achieves, in one vessel, the synthesis of substituted 5,6,7,8-tetrahydrothieno[2,3-b]quinolines (IX) (see Experimental section).

The IR spectra of the synthesized compounds I, VII show characteristic absorption bands for a conjugated cyano group at 2220 cm^{-1} and the PMR spectra show signals for the protons of the tetramethylene fragment at δ 2.55-2.90 (4H, m, $(CH_2)_2$) and at 1.60-1.75 (4H, m, $(CH_2)_2$), the heteroaromatic substituent in the corresponding region (Table 2), and signals for the XCH_2 group protons at δ 3.98-4.80 ppm.

The structure of compound Ii was confirmed by x-ray structural analysis, the results of which will be published later.

EXPERIMENTAL

PMR spectra were recorded on a Bruker WP-100 SY (100 MHz) using DMSO-D_6 solvent and TMS internal standard. IR spectra were taken on an IRS-29 machine using Vaseline oil. Monitoring of the reaction course and the purity of the materials was carried out using TLC on Silufol UV-254 plates (eluent acetone–heptane, 3:5).

Hetarylmethylenecyanothioacetamides IIIa-c,e were prepared by a known method [14].

4-Hetaryl-3-cyano-5,6,7,8-tetrahydoquinolin-2(1H)-thiones VIIa-c,e were prepared by the method reported in [11].

2-Alkylthio(seleno)-4-het-3-cyano-5,6,7,8-tetrahydroquinolines (Ia-q). A. A mixture of enamine II (1.67 g, 10 mmole) and the substituted acrylonitrile IIIa-e (1.78 g, 10 mmole) in absolute ethanol (20 ml) was stirred at 20°C for 4 h (in the case of IIId, in an argon atmosphere). Aqueous KOH solution (10%, 5.6 ml, 10 mmole) was added to the reaction product, compound IVa-q after a further 5 min, and stirring was continued for 5 h. The precipitate was filtered, washed with water, ethanol, and hexane to give the quinolines (Ia-q) (for data, see Tables 1, 2).

B. Aqueous KOH solution (10%, 5.6 ml, 10 mmole) was added with stirring to a suspension of the quinolinechalcogenone VIIa-e (10 mmole), and the halide IVa-q (10 mmole) was added after a further 3 min. After 4 h, the reaction mixture was diluted with water (10 ml) and the precipitate formed was filtered off. The obtained Ia-q were identical in melting point and IR spectra to samples synthesized by method A (Tables 1, 2).

2-Furylmethylenecyanoselenoacetamide (IIId). N-Methylmorpholine (3 drops) was added to a suspension of furfurol (0.83 ml, 10 mmole) and cyanoselenoacetamide (1.47 g, 10 mmole) in absolute ethanol (10 ml) under an argon atmosphere. The reaction product was stirred for 1 h and held for a further 24 h at 20°C. The precipitate was filtered off to give IIId (1.25 g, 70%) as ruby crystals with mp 142-144°C. IR spectrum: 3240-3335 (NH_2), 2215 cm^{-1} (CN). PMR spectrum: 10.86 and 10.08 (2H, two s, NH_2); 8.20 (1H, s, CH=); 8.06 (1H, s, 5-H_{Het}); 7.5 (1H, d, 4-H_{Het}); 6.85 ppm (1H, s, 3-H_{Het}). Found, %: C 42.78; H 2.81; N 12.30; Se 34.85. $C_8H_6N_2OSe$. Calculated, %: C 42.69; H 2.69; N 12.44; Se 35.08.

4-(2-Furyl)-3-cyano-5,6,7,8-tetrahydroquinoline-2(1H)-selenone (VIId). A mixture of enamine II (1.67 g, 10 mmole) and selenoamide IIId (1.78 g, 10 mmole) in absolute ethanol (20 ml) was stirred for 4 h at 20°C in an argon atmosphere. The precipitate was filtered and washed with ethanol and hexane to give selenone VIId (2.1 g, 69%) with mp 205-207°C. IR spectrum: 2215 cm^{-1} (CN). PMR spectrum: 7.99 (1H, s, 5-H_{Het}); 7.07 (1H, m, 4-H_{Het}); 6.73 (1H, m, 3-H_{Het}); 2.84 (2H, m, CH_2); 2.50 (2H, m, CH_2); 1.71 ppm (4H, m, $(CH_2)_2$). Found, %: C 55.63; H 4.13; N 9.01; Se 25.85. $C_{14}H_{12}N_2OSe$. Calculated, %: C 55.46; H 3.99; N 9.24; Se 26.04.

TABLE 1. Parameters for Compounds Synthesized Ia-q

Compound	Empirical formula	Found, % / Calculated, %				Mp, °C (solvent for crystallization)	IR spectrum, ν, cm^{-1}		Yield, % (method A/B)
		C	H	N	S(Se)		C ≡ N	C=O	
1	2	3	4	5	6	7	8	9	10
Ia	$C_{22}H_{17}BrN_2O_2S$	58,45 / 58,29	3,89 / 3,78	5,99 / 6,18	6,80 / 7,07	128...130 (AcOH)	2220	1680	82 / 78
Ib	$C_{15}H_{14}N_2OSe$	56,86 / 56,79	4,22 / 4,45	8,97 / 8,83	24,70 / 24,89	156...158 (i-PrOH)	2212	—	68 /70
Ic	$C_{26}H_{20}N_2O_2S_2$	68,52 / 68,40	4,64 / 4,42	6,02 / 6,14	14,11 / 14,04	190...192 (DMFA)	2218	1678	80 / 73
Id	$C_{16}H_{14}N_2O_2S_2$	58,01 / 58,16	4,35 / 4,27	8,59 / 8,48	19,22 / 19,41	135...137 (EtOH)	2220	1700	72 / 75
Ie	$C_{22}H_{20}N_2S_2$	70,38 / 70,18	5,54 / 5,35	7,28 / 7,44	16,80 / 17,03	118...120 (EtOH)	2220	—	81 / 83
If	$C_{20}H_{16}N_2OS_3$	60,65 / 60,58	4,11 / 4,07	7,25 / 7,06	24,03 / 24,26	123...125 (AcOH)	2219	1710	79 / 85
Ig	$C_{22}H_{18}N_2OS_2$	67,76 / 67,66	4,42 / 4,65	7,29 / 7,17	16,78 / 16,42	131...133 (AcOH)	2220	1700	82 / 80
Ih	$C_{17}H_{16}N_2O_2S_2$	59,39 / 59,28	4,74 / 4,68	7,95 / 8,13	18,50 / 18,62	124...126 (EtOH)	2222	1725	72 / 64

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
Ii	$C_{21}H_{18}N_2S_2$	69,70 69,58	4,84 5,01	7,82 7,73	17,64 17,69	142...144 (EtOH)	2219	—	78 / 88
Ij	$C_{25}H_{18}N_2O_3S_2$	65,55 65,48	4,11 3,96	5,93 6,11	14,04 13,98	218...220 (1-BuOH)	2224	1700	79 / 81
Ik	$C_{16}H_{15}N_3OS_2$	58,15 58,33	4,40 4,59	12,89 12,76	19,54 19,47	138...140 (1-BuOH)	2216	1654	77 / 71
Il	$C_{18}H_{17}N_3O_2S$	63,51 63,70	4,86 5,05	12,43 12,38	9,60 9,45	154...156 (EtOH)	2218	1738	80 / 77
Im	$C_{17}H_{16}N_4OS$	63,09 62,94	5,15 4,97	17,10 17,27	9,74 9,88	88...90 (EtOH)	2218	1680	75 / 82
In	$C_{23}H_{18}ClN_3OS$	65,84 65,79	4,13 4,32	10,15 10,01	7,89 7,64	170...172 (AcOH)	2217	1684	74 / 60
Io	$C_{21}H_{17}N_3OS_2$	64,58 64,42	4,49 4,38	10,65 10,73	16,21 16,38	180...182 (AcOH)	2230	1664	85 / 82
Ip	$C_{23}H_{21}N_3S$	74,45 74,36	5,57 5,70	11,45 11,31	8,53 8,63	153...155 (AcOH)	2212	—	71 / 69
Iq	$C_{28}H_{21}ClN_2O_2S$	69,20 69,34	4,14 4,36	5,89 5,78	6,78 6,61	195...197 (1-BuOH)	2218	1680	86 / 82

TABLE 2. PMR Spectra of Compounds Synthesized Ia-q

Compound	Chemical shift, δ, ppm					
	6- and 7-CH_2, m	5-CH_2, m	8-CH_2, m	Het	XCH_2, s	Z
Ia	1,63	2,49	2,65	6,75 (1H, m, 3-H); 7,04 (1H, d, 4-H); 8,02 (1H, m, 5-H)	4,80	8,13 (1H, s); 7,62 (3H, m)
Ib	1,73	2,65	2,91	6,73 (1H, m, 3-H); 7,04 (1H, d, 4-H); 7,99 (1H, d, 5-H)	2,46	—
Ic	1,68	2,53	2,78	7,25...7,60 (5H, m, 5-Ph); 8,04 (1H, d); 8,17 (1H, d)	4,73	7,20 (2H, m, 3-H and 5-H); 7,87 (1H, m, 4-H)
Id	1,66	2,24	2,86	7,83 (1H, d, 4-H); 7,25 (2H, m, 3-H and 5-H)	4,04	13,20 br. s
Ie	1,80	2,90	3,25	7,85 (1H, m, 4-H); 7,23 (2H, m, 3-H and 5-H)*	4,54	2,45 (3H, s, CH_3); 7,23 (4H, m, Ar)*
If	1,63	2,51*	2,51*	7,28 (2H, m, 5-H and 3-H)*; 7,86 (1H, d. d, 4-H)	4,77	7,28 (1H, m, 5-H)*; 8,09 (1H, d, 4-H); 8,23 (1H, d, 3-H)
Ig	1,60	2,48*	2,48*	7,27 (2H, m, 3- and 5-H); 7,84 (1H, d. d, 4-H)	4,83	7,63 (3H, m, Ph); 8,07 (2H, m, Ph)
Ih	1,69	2,50	2,83	7,27 (2H, m, 3- and 5-H); 7,82 (1H, d. d, 4-H)	4,08	3,67 (3H, s, OCH_3)
Ii	1,74	2,51 t	2,98 t	7,26 (2H, m, 3- and 5-H); 7,83 (1H, d. d, 4-H)	4,51	7,30...7,65 (5H, m, Ph)
Ij	1,67	2,50	2,71	7,27 (2H, m, 3- and 5-H); 8,74 (1H, m, 4-H)	4,80	7,35...8,12 (5H, m, coumarinyl)
Ik	1,76	2,55 t	2,93 t	7,31 (2H, m, 3- and 5-H); 7,88 (1H, d. d, 4-H)	3,97	7,19 and 7,62 (2H, two br. s, NH_2)
Il	1,69	2,32	2,85	8,75 (2H, d, 2- and 6-H); 7,44 (2H, d, 3- and 5-H)	4,11	3,67 (3H, s, OCH_3)
Im	1,71	2,34 t	2,98 t	8,77 (2H, d, 2- and 6-H); 7,44 (2H, d, 3- and 5-H)	3,98	7,63 and 7,20 (2H, two s, NH_2)
In	1,60	2,27	2,51	8,74 (2H, d, 2- and 6-H); 7,43 (2H, d, 3- and 5-H)	4,82	8,10 and 7,43 (4H, two d, Ar)
Io	1,62	2,29	2,52	8,77 (2H, d, 2- and 6-H); 7,45 (2H, d, 3- and 5-H)	4,80	7,33 (1H, m, 4-H); 8,08 (1H, d, 3-H); 8,21 (1H, d, 5-H)
Ip	1,71	2,31	3,01 t	8,73 (2H, d, 2- and 6-H); 7,42 (2H, d, 3- and 5-H)	4,54	2,39 (3H, s, CH_3); 7,18 (4H, m, Ar)
Iq	1,70	2,56	2,78	7,22 (2H, m); 7,35 (3H, m, 5-Ph); 7,87 (2H, m, 5-Ph)	4,80	8,09 and 8,60 (4H, two d, Ar)

3-Amino-4-[2-(5-phenylfuryl)]-2-(4-chlorobenzoyl)-5,6,7,8-tetrahydrothieno[2,3-b]-quinoline (IXa) was synthesized by method A reported for quinolines I using IVq (2.34 g, 10 mmole) and aqueous KOH solution (10%, 11.2 ml, 20 mmole) to give the thienoquinoline IXa (3.27 g, 66%) with mp 165-167°C (from 1-butanol). IR spectrum: 3280, 3465 cm^{-1} (NH_2). PMR spectrum: 7.78 (2H, d, H_{Ar}); 7.65 (2H, d, H_{Ar}); 7.50 (5H, m, H_{Ph}); 7.00 (1H, m, 3-H_{Het}); 7.28 (1H, m, 4-H_{Het}); 7.15 (2H, s, NH_2); 3.05 (2H, t, CH_2); 2.73 (2H, t, CH_2); 1.81 ppm (4H, m, $(CH_2)_2$). Found, %: C 69.22; H 4.10; N 5.92; S 6.69. $C_{28}H_{21}ClN_2O_2S$. Calculated, %: C 69.34; H 4.36; N 5.78; S 6.61.

3-Amino-2-(4-methylbenzoyl)-4-(2-thienyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline (IXb). A. Compound IXb was prepared by method A as described for quinolines I using the halide IVr (2.13 g, 10 mmole) and aqueous KOH solution (10%, 11.2 ml, 20 mmole) to give IXb (1.38 g, 65%) with mp 170-172°C (1-butanol). IR spectrum: 3300, 3480 cm^{-1} (NH_2). PMR spectrum: 7.94 (1H, d, 5-H_{Het}); 7.66 (2H, d, H_{Ar}); 7.32 (2H, d, H_{Ar}); 7.28 (2H, m, 3- and 4-H_{Het}); 6.79 (2H, br s, NH_2); 2.99 (2H, q, CH_2); 2.52 (2H, m, CH_2); 2.40 (3H, s, CH_3); 1.76 ppm (4H, m, $(CH_2)_2$). Found, %: C 68.39; H 5.19; N 6.77; S 15.71. $C_{23}H_{20}N_2OS_2$. Calculated, %: C 68.29; H 4.98; N 6.92; S 15.85.

B. Aqueous KOH solution (10%, 2.8 ml, 5 mmole) was added to a suspension of Ir (2.4 g, 5 mmole) in DMF (10 ml). The reaction product was stirred for 4 h at 20°C, diluted with water (10 ml), and the precipitate filtered off to give IXa (1.5 g, 62%), identical to a sample synthesized by method A (a mixed sample did not depress the melting point).

This work was carried out with the financial support of the Russian Fund for Fundamental Research (project No. 96-03-32012a).

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