

Syntheses of Some New Five-Membered Heterocycles Containing Selenium and Tellurium

Jirí Šibor and Pavel Pazdera

Department of Organic Chemistry, Faculty of Science, Masaryk University, CZ-611 37 Brno, Czech Republic; Fax: +42-5-412-112-14 (sibor@chemi.muni.cz)

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Abstract

The syntheses of some new chalcogenazole **1** and chalcogenophene **2**, **3** derivatives under conventional Gewald's conditions [1–4], by the action of ultrasound and focused microwave irradiation is reported. It was found that although ultrasound accelerated the described reaction significantly, the focused microwave irradiation manifested itself even more significantly.

Keywords: chalcogenazole, chalcogenophene, synthesis acceleration, ultrasound, microwave radiation

Introduction

The synthesis of 5-amino-3-thioxo-1,2-dithiol-4-carboxylic acid [1], 5-amino-3-R-2-thioxothiazole-4-carboxylic acids [2] and 2-amino-4,5-di-R-thiophene-3-carboxylic acids functional derivatives [3, 4] using elementary sulfur as a reagent has been already described by Gewald. These compounds were prepared by the reaction of malonic acid functional derivatives (malononitrile, ethyl cyanoacetate and cyanoacetamide) and elemental sulfur in the presence of a base either with carbon disulfide (in the case of dithiols), and phenyl-, methyl- and allylthiocyanates (in the case of thiazole skeleton syntheses) or with oxo compounds containing α -methyl or α -methylene group in the case of thiophene derivatives. During the described reactions heat was liberated. The yields of the reactions

were found to be dependent on, in addition to the skeleton character, the acidity of the malonic acid functional derivative used. In the case of dithiol derivatives the yields were 20–30%, for thiazole skeletons they ranged between 70–85% and for the thiophenes between 35–90%.

It was found that the mechanism of the syntheses presented probably starts with the reaction of malonic acid functional derivative with carbon disulfide, the R-isothiocyanate and oxo compound, respectively [1–4]. In the next step, the product of addition or condensation reacts with elementary sulfur in the presence of a base under formation of the corresponding skeleton. The reaction pathway of this process was studied for dithiol [1, 5] and thiophene [3, 4] formation.

Isomeric 4-amino-2-phenyl-5-R-thiophene-3-carbonitriles and analogical selenophenes were synthesized in one step by reaction β -chloro- α -cyano-cinnamitrile and acceptor-substituted chloromethane with sodium sulfide and sodium selenide, respectively [6].

We described the synthesis selenium and tellurium analogues [5] of the dithiols mentioned above by Gewald's

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method [1]. The chalcogenols were prepared from elementary selenium and tellurium. We used the ultrasound for intensification of reactions. The reaction time was shorter and yields higher in comparison with the conventional conditions.

We wanted to prepare analogous selenium and tellurium compounds of chalcogenazole and chalcogenophene derivatives, and other new sulfur, selenium and tellurium compounds containing further structural unit. They were in the case of chalcogenazole **1** derivatives with acyl substituents (pivaloyl, benzoyl) and in the case of chalcogenophenes **2**, **3** derivatives with a fused bornane skeleton. The target of our interest in the synthesis of these new compounds was its perspective application for further synthesis of new fused heterocyclic skeletons and their further screening for pharmacological activity.

Results and Discussion

To begin with, we prepared 4-benzoyl and 4-pivaloyl substituted 5-amino-3-R-2-thioxothiazole-4-carboxylic acid functional derivatives, e.g. nitrile, ethyl ester and amide by the above mentioned Gewald's procedure [2]. The experimental aspects of the syntheses (temperature, reaction times and yields) were in accordance with the data presented by Gewald. The only difference was that the procedure applied to the synthesis of selenium and tellurium analogues proceeded very slowly. The observed reaction times, reported in Table 1, increased from sulfur to tellurium analogues. The highest yields of the individual reactions were obtained for derivatives containing sulfur (Scheme 1) and continuously decreased from the selenium to the tellurium derivatives in contrast to the reaction times (Table 1, 2; X = S).

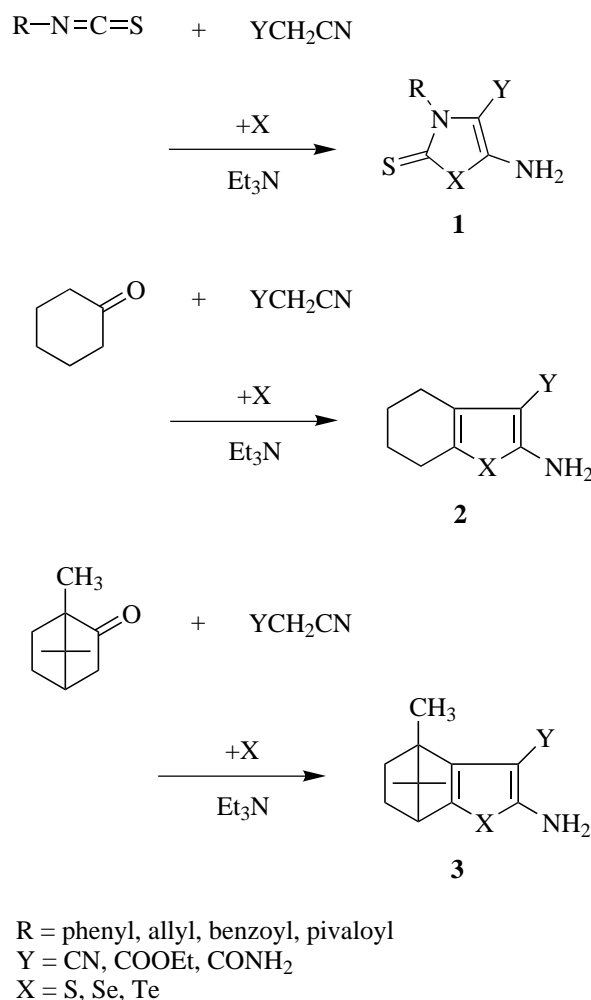
As noted above, the series of 5-amino-3-R-2-thioxochalcogenazole-4-carboxylic acid functional derivatives **1** were synthesized in a similar manner by the action of sulfur, selenium and tellurium on a mixture of the presented malonic acid functional derivatives with corresponding R-isothiocyanate (R = phenyl, allyl, benzoyl and pivaloyl). The reactions were carried out in dimethylformamide solution in the presence of triethylamine as a base. With sulfur, the reactions proceeded well at room temperature, but in the case of selenium and tellurium derivatives heterogeneous mixtures required reflux after the starting exothermic part of the reaction.

The course of all the preparations was monitored by TLC. It was shown that, during the reaction, only one intermediate (probably an adduct of the malonic acid functional derivative of the initial R-isothiocyanate or carbonyl compound) was formed which changed to the final and side reaction products. In all cases R_F values for all the final products ranged between 0.6–0.8. For very polar concomitant products, they were about 0 and for intermediates in the range of 0.2–0.4.

Reactions were stopped when the intermediate disappeared. Then the reactions mixtures were filtered with activated charcoal to eliminate residual chalcogen and other impurities formed in competitive reactions. The desired products were precipitated with crushed ice and recrystallized from ethanol.

Our approach to Gewald's system [3, 4] also included the synthesis of 2-amino-4,5-(butan-1,4-diyl)-chalcogenophene-3-carboxylic acid functional derivatives, i.e. nitrile, ethyl ester and amide, where the chalcogen is selenium and tellurium. We also wanted to prepare corresponding chalcogenophene rings with fused bornane.

The chalcogenophene, in turn, was formed via the reaction of malonic acid functional derivatives with cyclohexanone in the presence of the corresponding chalcogen. This strategy was based on the synthesis previously used by Gewald [3, 4] and the reaction conditions were chosen according to his information. However, we used dimethylformamide as the solvent and triethylamine or morpholine as the base. In the case of selenium and tel-



Scheme 1. Synthesis of title compounds **1**, **2** and **3**.

Table 1. Reaction time and yields for chalcogenazoles 1.

Product	R	Y	X	Reaction time/Yield,%		
				"classic"	US action	MW action
1.1.a	Ph	CN	S	60 min/80	—	—
1.1.b	Ph	COOEt	S	80 min/85	—	—
1.1.c	Ph	CONH ₂	S	90 min/75	—	—
1.2.a	Ph	CN	Se	28 h/70	4 h/82	4 min/92
1.2.b	Ph	COOEt	Se	30 h/65	5 h/80	5 min/91
1.2.c	Ph	CONH ₂	Se	35 h/65	7 h/80	7 min/91
1.3.a	Ph	CN	Te	7d/55	2d/78	10 min/90
1.3.b	Ph	COOEt	Te	7d/55	3d/76	11 min/88
1.3.c	Ph	CONH ₂	Te	7d/55	3d/76	11 min/88
1.4.a	allyl	CN	S	90 min/80	20 min/85	—
1.4.b	allyl	COOEt	S	120 min/75	30 min/89	—
1.4.c	allyl	CONH ₂	S	180 min/75	35 min/88	—
1.5.a	allyl	CN	Se	35 h/70	6 h/82	5 min/93
1.5.b	allyl	COOEt	Se	40 h/68	7 h/79	6 min/92
1.5.c	allyl	CONH ₂	Se	45 h/72	7 h/78	6 min/93
1.6.a	allyl	CN	Te	10d/56	2d/68	12 min/92
1.6.b	allyl	COOEt	Te	11d/53	2.5d/66	14 min/90
1.6.c	allyl	CONH ₂	Te	12d/52	2.5d/67	14 min/90
1.7.a	benzoyl	CN	S	40 min/85	—	—
1.7.b	benzoyl	COOEt	S	60 min/83	—	—
1.7.c	benzoyl	CONH ₂	S	70 min/84	—	—
1.8.a	benzoyl	CN	Se	24 h/68	3 h/79	4 min/94
1.8.b	benzoyl	COOEt	Se	28 h/62	4 h/76	4.5 min/92
1.8.c	benzoyl	CONH ₂	Se	30 h/62	4 h/76	4.5 min/92
1.9.a	benzoyl	CN	Te	8d/56	2d/74	10 min/89
1.9.b	benzoyl	COOEt	Te	10d/52	2.5d/68	12 min/87
1.9.c	benzoyl	CONH ₂	Te	10d/52	2.5d/67	12.5 min/87
1.10.a	pivaloyl	CN	S	50 min/83	—	—
1.10.b	pivaloyl	COOEt	S	70 min/82	—	—
1.10.c	pivaloyl	CONH ₂	S	80 min/80	20 min/87	—
1.11.a	pivaloyl	CN	Se	28 h/72	5 h/84	5 min/96
1.11.b	pivaloyl	COOEt	Se	30 h/70	5.5 h/83	5.5 min/94
1.11.c	pivaloyl	CONH ₂	Se	31 h/69	5.5 h/81	5.5 min/94
1.12.a	pivaloyl	CN	Te	6d/61	1.5d/72	9 min/89
1.12.b	pivaloyl	COOEt	Te	7d/56	2d/68	12 min/84
1.12.c	pivaloyl	CONH ₂	Te	7.5d/55	2d/68	12 min/86

Table 2. Reaction time and yields for chalcogenophenes **2**, **3**.

Product	R	Y	X	Reaction time/Yield		
				"classic"	US action	MW action
2.1.a	—	CN	S	30 min/98	—	—
2.1.b	—	COOEt	S	40 min/95	—	—
2.1.c	—	CONH ₂	S	60 min/96	—	—
2.2.a	—	CN	Se	24 h/87	6 h/91	4 min/96
2.2.b	—	COOEt	Se	28 h/86	7 h/90	5.5 min/95
2.2.c	—	CONH ₂	Se	30 h/86	7.5 h/89	6 min/96
2.3.a	—	CN	Te	10d/72	2d/84	90 min/96
2.3.b	—	COOEt	Te	11d/68	3d/81	90 min/92
2.3.c	—	CONH ₂	Te	12d/64	3d/81	90 min/90
3.1.a	—	CN	S	60 min/98	20 min/98	—
3.1.b	—	COOEt	S	70 min/96	20 min/98	—
3.1.c	—	CONH ₂	S	70 min/96	20 min/98	—
3.2.a	—	CN	Se	2d/76	11 h/84	15 min/92
3.2.b	—	COOEt	Se	2d/72	12 h/80	15 min/89
3.2.c	—	CONH ₂	Se	2.5d/72	12 h/80	15 min/89
3.3.a	—	CN	Te	21d/71	6d/76	120 min/90
3.3.b	—	COOEt	Te	25d/68	7d/73	120 min/90
3.3.c	—	CONH ₂	Te	25d/68	7d/70	120 min/90

lurium derivatives the heterogenous mixtures had to be refluxed after the exothermic condensation step. The end of the reaction was monitored by TLC. The products were separated by the above-mentioned procedure.

The purity of all the synthesized compounds was monitored by TLC and C, N, H and Se elemental analyses. Their structures were supported by the comparison of their FTIR spectra with one of Gewald's standards, in some cases ¹H- and ¹³C-NMR spectra were also measured.

The synthesis of corresponding fused bornane skeleton **3** was carried out in a similar way. However, instead of cyclohexanone, we used camphor. In this case even elemental sulfur is much slower.

As it is evident from Tables 1 and 2, the reaction time varies significantly between the individual series of compounds mentioned. In the case of structure **1**, it ranges from 40 min to 12 days using the "classic" method. On the other hand, the compounds **2** and **3** have time range between 30 min and 25 days with Gewald's method. The shortest reaction times were observed for compounds containing sulfur and nitrile groups in the molecules. The reaction time increased from sulfur to selenium and tellurium and also from cyanoderivatives to ethyl ester derivatives and amido derivatives. In the case of structure **1**, the acyl derivatives reacted faster than the corresponding phenyl- and allyl

analogues. The reaction time of chalcogenophene **2**, **3** formation from cyclohexanone was slower than the formation of the corresponding fused bornane skeleton.

Our aim was to find better reaction conditions in order to shorten the reaction time for some compounds significantly. Our experimental results and those mentioned above indicate that intensification is necessary in the second reaction step, i.e. the reaction of the intermediary adduct with the chalcogenating agent. It is evident that reactivity in the course of these syntheses decreases from sulfur to tellurium. The activity of chalcogens was observed to decrease in this order generally. In the cases of reactions with selenium and tellurium, the mixture is heterogenous because both these chalcogenes are not soluble in the reaction mixtures in contrast to sulfur. Some methods are known to accelerate the reaction. They are ultrasound [7] and focused microwave [8] irradiation in general. For that reason we attempted their use as a means for decreasing the reaction time.

At first we used ultrasound to accelerate the reactions. We prepared the reaction mixture in accordance with the above-mentioned procedure. This mixture was placed in the ultrasound apparatus. The reaction was carried out at room temperature. When the mixture was exposed to ultrasound for the times presented in Tables 1 and 2.

We found that the reaction rate increased significantly and the reaction time decreased from three to seven times in comparison to the conventional method. In the case of the chalcogenophene derivatives the increase was not so significant. The yields of these reactions were also higher than those obtained by the "classic" method. The yields increased by about 10% for the crude products and their purity was better. The yields were higher than those when using the conventional method. From Table 1, it is evident that some compounds still required very long reaction times and that further improvements in yields are needed. For these reasons we chose another method which might also increase the rate and yields.

We used microwave irradiation for the reaction. The starting reaction mixtures were prepared as mentioned above. This choice was shown to be very effective. In this way, we were able to obtain products very easily. The reaction temperature was kept at 80 °C during the whole reaction time by microwave source (during the first two minutes the temperature increased from room temperature to 80 °C) during irradiation. The reaction mixture was stirred by a mechanical agitator. The reaction times for the microwave preparation are presented in Tables 1 and 2.

The reaction rate was very fast under these conditions. Table 1 shows that microwave irradiation was very efficient and the most efficient method of accelerating the reaction. The reaction time was shortened from the 60 min–25 days of the "classic" method to 4 min–120 min, which was about 300% on an average. The average decrease was about 60% in comparison to using ultrasound. The yields also increased in the case of focused microwave irradiation application. The products isolated were 80–95% of the theoretical yield. The purity of the separated compounds was sometimes so high that their crystallization was in some cases unnecessary after the above-mentioned procedure of separation had been carried out.

Experimental Section

General Details

Chemicals and reagents were obtained from Fluka Chemie Co. and used without purification. Melting points were measured on a Boetius Rapido PHMK 79/2106 (Wägetechnik) instrument. The purity of compounds was checked by CHN elemental analyses on a 1102 (Erba) instrument, by determination of selenium on an ICP AES 7500 (Unicam) spectrometer and the values found compared with the calculated ones. TLC was carried out on Silufol UV 254 plates (Kavalier, Votice) with diethylether as the eluent. The detection with Fluotest Universal (Quartzlampen, Hanau) or with iodine vapours. FTIR spectra were obtained using a Genesis (Unicam) spectrometer

using potassium bromide pellets. ¹H-NMR and ¹³C-NMR spectra were measured on an Avance DRX-500 (Bruker) spectrometer. The chemical shifts (δ, ppm) were referenced to tetramethylsilane as the internal standard or to the solvent signal (deuteriochloroform, hexadeuterodimethyl sulfoxide). Spectral width: 9000 Hz for ¹H, 27500 Hz for ¹³C. The ultrasonic reactions were tested by a Tesson 10 (Tesla) apparatus with a frequency of 36–42 kHz at 250 W. The reactions supported by focused microwaves were realized on Synthwave 402 (Prolabo). Microwave power was 300 W and the frequency 2450 MHz.

General Procedure of the Syntheses

5-Amino-3-R-2-thioxochalcogenazole-4-carboxylic acid functional derivatives 1

Gewald's Method. Triethylamine (6 ml) was added dropwise under stirring to the solution of corresponding malonic acid derivative (0.05 mol), R-isothiocyanate (0.05 mol) and corresponding chalcogen (0.06 mol) in DMF (6 ml). The reaction temperature than 50 °C. The course of the reaction was monitored by TLC. When the reaction was finished, the mixture was filtered with charcoal and poured onto crushed ice. The precipitation formed was filtered off and washed with water and cold methanol. The product was crystallized from aqueous dimethylformamide.

2-Amino-4,5-(butan-1,4-diyl)-chalcogenophene-3-carboxylic acid functional derivatives 2 and 2-amino-4,5-(1,2,2-trimethylcyclopentane-1,3-diyl)-chalcogenophene-3-carboxylic acid functional derivatives 3

Gewald's Method. To the solution containing the corresponding malonic acid derivative (0.05 mol), cyclohexanone or camphor (0.05 mol) and corresponding chalcogen (0.06 mol) in DMF (6 ml), was under stirring triethylamine (6 ml) dropwise added. In the cases of reactions with selenium or tellurium the mixture has to be refluxed. When the reaction was finished (TLC monitoring) the mixture was filtered with charcoal and poured into crushed ice. The formed crystals were filtered off and washed with water. The products **2** were crystallized from aqueous dimethylformamide and products **3** from ethanol.

Application of Ultrasound and Focused Microwaves. The reaction mixtures prepared by the mentioned above procedures were placed into an ultrasound apparatus or a microwave unit. The reaction times for the ultrasound and microwave action are presented in the Table 1. Products were isolated using the same procedures already mentioned.

Examples of prepared compounds

5-Amino-3-pivaloyl-2-thioxothiazole-4-carbonitrile **1.10.a**

mp 115–118 °C.

IR 3346, 3306, 3193, 1612 (NH), 2207 (CN), 1687 (NCO), 1050 (C = S) cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3) 1.45 (9H, *s*, *t*-Bu), 6.73 (2H, *s*, NH_2).

$^{13}\text{C-NMR}$ (CDCl_3) 30.58, 42.14, 98.21, 115.99, 116.57, 185.18, 191.62.

Ethyl 5-Amino-3-benzoyl-2-thioxoselenazole-4-carboxylate **1.8.b**

mp 140–143 °C.

IR 3308, 3223, 3157, 1605 (NH), 1710, 1240 (COOC), 1649 (NCO), 1023 (C = S) cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3) 1.18 (3H, *t*, J 7.1 Hz, OCH_2CH_3), 3.34 (2H, *q*, J 7.1 Hz, OCH_2CH_3), 8.27–8.49 (5H, *m*, ArH), 9.05 (2H, *s*, NH_2).

Ethyl 5-Amino-3-benzoyl-2-thioxothiazole-4-carboxylate **1.7.b**

mp > 350 °C.

IR 3230, 3152, 3034, 1605 (NH), 1712, 1257 (COOC), 1672 (NCO), 1045 (C = S) cm^{-1} .

Ethyl 2-Amino-4,5-(butan-1,4-diyl)selenophene-3-carboxylate **2.2.b**

mp 158–160 °C.

IR 3412, 3349, 3265, 1647 (NH), 1754, 1713, 1235 (COOC), 1664 (NCO) cm^{-1} .

2-Amino-4,5-(butan-1,4-diyl)tellurophene-3-carbonitrile **2.3.a**

mp 193–197 °C.

IR 3429, 3340, 3248, 1648 (NH), 2208 (CN) cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3) 1.75–1.84 (4H, *m*, CH_2), 2.45–2.46 (2H, *m*, CH_2), 2.59–2.60 (2H, *m*, CH_2), 5.05 (2H, *s*, NH_2).

$^{13}\text{C-NMR}$ (CDCl_3) 22.09, 23.83, 26.07, 26.39, 90.31 (J 37 Hz), 116.34 (J 44 Hz), 124.84 (J 103 Hz), 133.08 (J 37 Hz), 164.80 (100 Hz).

2-Amino-4,5-(butan-1,4-diyl)tellurophene-3-carboxamide **2.3.c**

mp >350 °C.

IR 3370, 3320, 3179, 3101, 1624 (NH), 1734, 1546, 1366 (NHCO) cm^{-1} .

2-amino-4,5-(1,2,2-trimethylcyclopentane-1,3-diyl)-thiophene-3-carbonitrile **3.1.a**

mp 251–252 °C.

IR 3409, 3320, 3182, 1613 (NH), 2189 (CN) cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3) 0.69 (3H, *s*, CH_3), 0.73 (3H, *s*, CH_3), 0.84 (3H, *s*, CH_3), 1.40–1.43 (4H, *m*, CH_2), 2.39–2.43 (H, *m*, CH), 6.87 (2H, *s*, NH_2).

$^{13}\text{C-NMR}$ (CDCl_3) 19.43, 19.94, 27.00, 29.90, 46.89, 57.54, 60.64, 68.13, 76.74, 115.72, 118.95, 152.74, 172.36.

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References

1. Gewald, K. *J. prakt. Chem.*, **1966**, 31, 214.
2. Gewald, K. *J. prakt. Chem.*, **1966**, 32, 26.
3. Gewald, K.; Schinke E.; Böttcher H. *Chem. Ber.*, **1966**, 99, 94.
4. Gewald, K.; Schinke E. *Chem. Ber.*, **1966**, 99, 2712.
5. Pazdera P.; Sibor J. *Folia Pharm. Universitatis Carolinae XVIII (Supplementum)*, **1995**, 179.
6. Gewald, K.; Hain U. *Monatsheft Chem.*, **1992**, 123, 455.
7. Mason T. J. *Advances in Sonochemistry*, JAI press, London, 1990 vol. 1, 1992 vol. 2, 1993 vol. 3.
8. Buchachenko A. L.; Frankevich E. L. *Chemical Generation and Reception of Radio- and Microwaves*, VCH Publishers, Inc., New York, 1994.