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A convenient method for the synthesis of 2-[(5-benzyl-1,3-thiazol-2-yl)imino]-1,3-thiazolidin-4-one derivatives

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ABSTRACT

It was found that the reaction of 2-chloroacetamido/chloropropioamido-5-benzylthiazole with potassium thiocyanate gave, via rearrangement, 2-[(5-benzyl-1,3-thiazol-2-yl)imino]-1,3-thiazolidin-4-ones.

4-Thiazolidinones are a class of important heterocycles that have attracted considerable attention because of their biological properties. They are represented in a well-known group of patented drugs and substances which possess hypoglycaemic, anti-inflammatory, choleretic, antitumor, diuretic and immunostimulant amongst other activities.[1,2]

General synthetic strategies for the preparation of this heterocycle include cyclisation reactions of thioureas or thiosemicarbazide derivatives, and cyclocondensation reactions of imines with α-mercapto acids.[2,3] In addition, recyclisation strategies have been reported.[3a] A method based on cyclisation of α-thiocyanatoamides has also been described.[3a,4] However, in this case, the structures of the products of the reaction were not discussed in detail. In particular, 2-[(thiazol-2-yl)imino]thiazolidin-4-ones and 2-imino-3-(thiazol-2-yl)thiazolidin-4-ones have been studied in recent years for the treatment of tumours and microbial diseases.[5,6] They have been prepared from chloroacetyl derivatives of 2-aminothiazoles **1** and the synthetic procedures were almost identical. Accordingly,[6] 2-imino-3-(thiazol-2-yl)thiazolidin-4-ones derivatives **2** are formed via the procedure shown in Scheme 1. The syntheses of α-thiocyanatoamides by way of a similar cyclisation were described earlier.[4] On the other hand, Geronikaki[5] reported the synthesis of compounds of type **3** using similar chemistry.

Clarification of this problem is very important especially for drug development. If the structures of compounds are not identified correctly, lead optimisation techniques such as SAR, QSAR, docking, etc can lead to false results.

Our interest in the synthesis of heterocyclic compounds of biological importance encouraged us to study the synthesis of new 2-iminothiazolidin-4-ones from 2-amino-5-benzylthiazoles **6**. It should be noted that thiazole derivatives bearing a substituted acylamino chain at C-2 and an arylmethyl moiety at C-5 have been the subject of research in recent years. They are reported as inhibitors of stearoyl-CoA desaturase-1[7] and demonstrate antiproliferative activity on the DU-145 human prostate carcinoma cell line.[8] Some new potentially active compounds were identified by application of a computer-aided drug design protocol based on a pharmacophoric model and docking simulations of the interactions between the ligands and the target protein.[9]

The starting 2-amino-5-benzylthiazoles **6a–c** were prepared by reaction of 3-aryl-2-chloropropanals **5a–c** with thiourea[10] (Table 1). Aldehydes **5** were synthesized from arenediazonium salts **4a–c** and acrolein under Meerwein reaction conditions. Aminothiazoles **6** reacted with chloroacetyl chlorides **7a**,**b** to form chloroacetamides **8a–f**.[11]

We next examined the reactions of compounds **8a–f** with potassium thiocyanate in acetonitrile, methanol, ethanol, acetone, DMF and DMSO. It was established that in all cases the reaction did not stop at the nucleophilic substitution stage. The α-thiocyanatoamides **9** underwent spontaneous cyclization/rearrangement to

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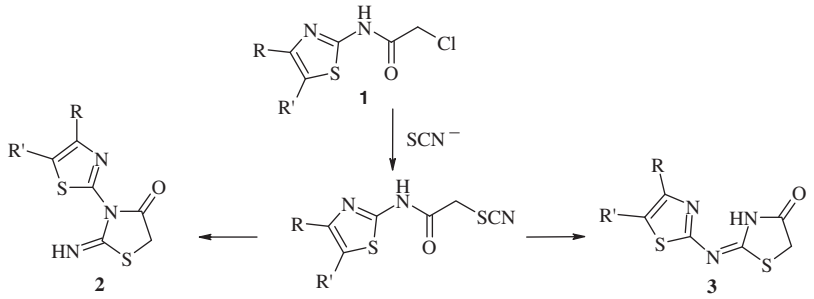
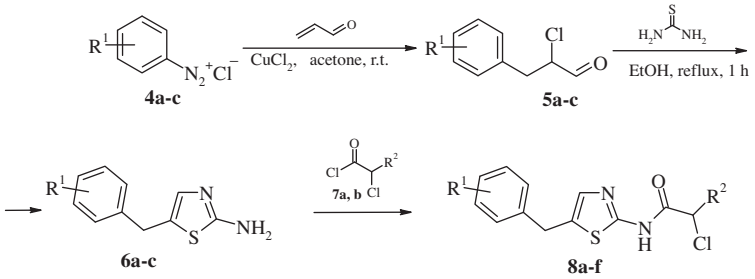


Scheme 1. Cyclisation of α-thiocyanatoamides.

Table 1
Preparation of *N*-(5-benzyl-1,3-thiazol-2-yl)-2-chloroacetamides **8a–f**



Compound	R^1	R^2	Yield (%)	Mp (°C)
8a	H	H	80	171
8b	3-Me	H	82	131
8c	4-Cl	H	85	159
8d	H	Me	70	141
8e	3-Me	Me	65	145
8f	4-Cl	Me	73	158

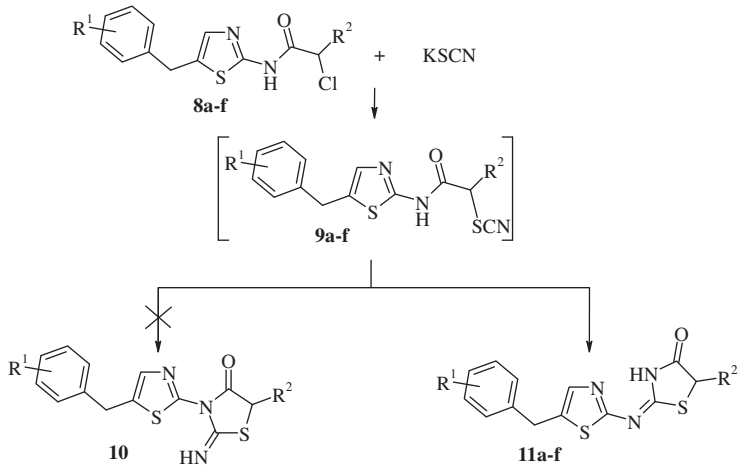
give thiazolidin-4-one derivatives **11a–f** (Scheme 2, Table 2).[12] Compounds **10** were not found.

The structure of compound **11f** was established by X-ray crystallography (Fig. 1).[13]

The X-ray analysis of **11f** showed that a hydrogen atom was attached to N3 which is in agreement with the structure containing a secondary amide in the thiazolidin-4-one ring and an exocyclic imine nitrogen. This finding is consistent with the crystallographic structure of compound **1** obtained both at 130 K and at room temperature. The appropriateness of this observation is supported

Table 2
2-[(5-Benzyl-1,3-thiazol-2-yl)imino]-1,3-thiazolidin-4-ones **11**

Compound	R^1	R^2	Yield (%)	Mp (°C)
11a	H	H	74	206
11b	3-Me	H	71	177
11c	4-Cl	H	75	200
11d	H	Me	78	154
11e	3-Me	Me	63	138
11f	4-Cl	Me	70	176



Scheme 2. Reactions of *N*-(5-benzyl-1,3-thiazol-2-yl)-2-chloroacetamides with potassium thiocyanate.

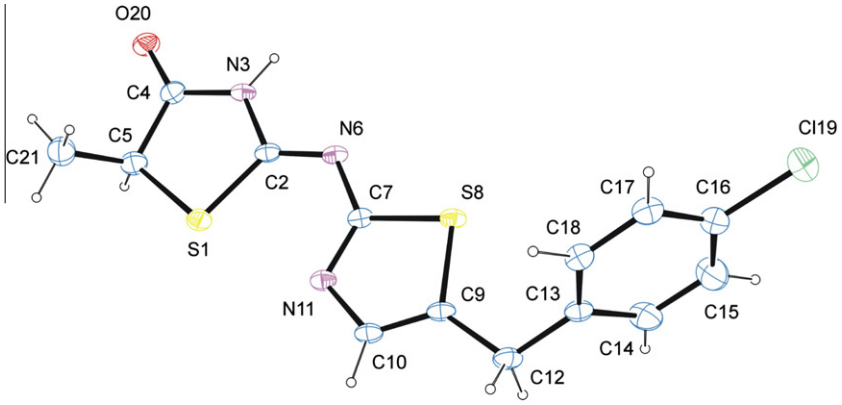


Figure 1. X-ray crystal structure (ORTEP plot) of **11f**.

by the values of the interatomic distances N3–C4 and C2–N3 [1.379(4) and 1.380(4) Å] as well as C2=N6 [1.292(4) Å] which are close to the mean values for the single bonds (*O*=)C–NH [1.357(2) Å] and NH–C(=*N*) [1.377(10) Å] as well as the double bond C=N [1.280(2) Å], respectively, acquired from two structures containing a 2-imino-1,3-thiazolidin-4-one moiety.[14,15]

The ^{1}H NMR spectra correlate with the crystallographically observed geometry. The spectra of the compounds **11a**–**f** showed a signal for the CH_2 protons at 3.96–4.20 ppm and a signal for the NH proton at 11.81–12.15 ppm. It should be noted that the resonance for the proton of the imino group at position 2 of the thiazolidinone ring for compounds **10** would be expected to occur at ~9 ppm.[16]

In summary, we have synthesized 2-[(5-benzyl-1,3-thiazol-2-yl)imino]-1,3-thiazolidin-4-ones by spontaneous cyclization/rearrangement of the intermediate α-thiocyanatoamides.

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References and notes

1. (a) Siddiqui, N.; Arshad, M. F.; Ahsan, W.; Alam, M. S. *Int. J. Pharm. Sci. Drug Res.* **2009**, *1*, 136–143; (b) Vinícius, M.; de Souza, N. *J. Sulfur Chem.* **2005**, *26*, 429–449.
2. Lesyk, R. B.; Zimenkovsky, B. S. *Curr. Org. Chem.* **2004**, *8*, 1547–1577.
3. (a) Singh, S. P.; Parmar, S. S.; Raman, K.; Stenberg, V. I. *Chem. Rev.* **1981**, *81*, 175–203; (b) Metwally, M. A.; Farahat, A. A.; Abdel-Wahab, B. F. *J. Sulfur Chem.* **2010**, *31*, 315–349.
4. Newcome, G. R.; Nayak, A. *Adv. Heterocycl. Chem.* **1979**, *25*, 93.
5. (a) Vicini, P.; Geronikaki, A.; Anastasia, K.; Incerti, M.; Zani, F. *Bioorg. Med. Chem.* **2006**, *14*, 3859–3864; (b) Geronikaki, A.; Eleftheriou, P.; Vicini, P.; Alam, I.; Dixit, A.; Saxena, A. K. *J. Med. Chem.* **2008**, *51*, 5221–5228; (c) c) Vicini, P.; Geronikaki, A.; Incerti, M.; Zani, F.; Dearden, J.; Hewitt, M. *Bioorg. Med. Chem* **2008**, *16*, 3714–3724.
6. (a) Zheng, W.; Degterev, A.; Hsu, E.; Yuan, J.; Yuan, Ch. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4932–4935; (b) Liu, H.-L.; Li, Z.; Anthonsen, T. *Molecules* **2000**, *5*, 1055–1061.
7. (a) Uto, Y.; Ogata, T.; Harada, J.; Kiyotsuka, Y.; Ueno, Y.; Miyazawa, Y.; Kurata, H.; Deguchi, T.; Watanabe, N.; Takagi, T.; Wakimoto, S.; Okuyama, R.; Abe, M.; Kurikawa, N.; Kawamura, S.; Yamato, M.; Osumi, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4151–4158; (b) Uto, Y.; Ogata, T.; Kiyotsuka, Y.; Miyazawa, Y.; Ueno, Y.; Kurata, H.; Deguchi, T.; Yamada, M.; Watanabe, N.; Takagi, T.; Wakimoto, S.; Okuyama, R.; Konishi, M.; Kurikawa, N.; Kono, K.; Osumi, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4159–4166.
8. Krasavin, M.; Karapetian, R.; Konstantinov, I.; Gezentsvey, Y.; Bukhryakov, K.; Godovykh, E.; Soldatkina, O.; Lavrovsky, Y.; Sosnov, A. V.; Gakh, A. A. *Arch. Pharm. Chem. Life Sci.* **2009**, *342*, 420–427.
9. Manetti, F.; Falchi, F.; Crespan, E.; Schenone, S.; Maga, G.; Botta, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4328–4331.
10. (a) Obushak, N. D.; Matiichuk, V. S.; Vasylyshin, R. Ya.; Ostapyuk, Yu. V. *Russ. J. Org. Chem.* **2004**, *40*, 383–389 (English translation from *Zh. Org. Khim*. **2004**, *40*, 412–417).
11. *Typical procedure for the synthesis of N-(5-benzyl-1,3-thiazol-2-yl)-2-chloroacetamides* **8a**–**f**. Chloroacetyl chloride **7** (0.05 mol) was added dropwise to a stirred solution of 2-amino-5-(arylmethyl)thiazole **6** (0.05 mol) and Et_3N (7 mL, 0.05 mol) in dry 1,4-dioxane (100 mL) at rt. The resulting solution was stirred for 1 h and then diluted with H_2O. The solid product was filtered, washed with H_2O and dried. Recrystallization from EtOH gave 2-chloroacetamido-5-(arylmethyl)thiazole **8** as a pale-yellow solid.
12. *Typical procedure for the synthesis of compounds* **11a**–**f**. A mixture of 2-chloroacetamido-5-(arylmethyl)thiazole **8a**–**f** (0.03 mol), KSCN (6.0 g, 0.06 mol) and dry acetone (100 mL) was stirred at room temperature for 20 h and then diluted with H_2O. The solid product was filtered, washed with H_2O and dried. Recrystallization from EtOH gave thiazolidinone **11** as a yellow solid. *2-[5-(4-Chlorophenyl)methyl-1,3-thiazol-2-ylimino]-5-methyl-thiazolidin-4-one* (**11f**): Yield 70%, mp 176 °C (EtOH); ^{1}H NMR (600 MHz, DMSO-d_6): 1.51 (d, 3H, J = 7.2, CH_3), 4.10 (s, 2H, CH_2), 4.27 (q, 1H, J = 7.2, CH), 7.29 (d, 2H, J = 8.4, 2,6-C_6H_4), 7.38 (d, 2H, J = 8.4, 3,5-C_6H_4), 7.39 (s, 1H, 4-H thiazole), 12.00 (br s, 1H, NH); ^{13}C NMR (150 MHz, DMSO-d_6): 18.0 (CH_3), 31.7 (CH), 43.8 (CH_2), 128.5, 130.2, 131.2, 134.4, 137.3, 139.0, 160.3, 168.5, 177.0; Anal. Calcd for $C_{14}H_{12}ClN_3OS_2$: C, 49.77; H, 3.58; N, 12.44. Found: C, 49.87; H, 3.52; N, 12.50.
13. Crystallographic data for **11f**: Empirical formula: $C_{14}H_{12}ClN_3OS_2$, formula weight: 337.84, colorless lath crystals, crystal system: monoclinic, space group: *C*2/*c*, a = 32.0442(18), b = 5.4312(2), c = 18.6559(11) Å, β = 115.152(7)°, V = 2939.0(3) Å^3, Z = 8, D_{calc} = 1.527 g/cm^3. A colorless crystal (EtOH) (0.25 × 0.21 × 0.02 mm) was used to record 26307 (Cu*K*α-radiation, θ_{max} = 75.6°) intensities on a SuperNova diffractometer. The supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ (UK), Tel.: (+44) 1223/336 408, Fax: (+44) 1223/336 033, e-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk (deposition No. CCDC 791941).
14. Entenmann, G.; Eckle, E.; Stezowski, J. J. *Phosphorus Sulfur* **1978**, *4*, 303.
15. Ramachandran, R.; Rani, M.; Kabilan, S. *Acta Cryst.* **2009**, *E65*, o584.
16. Obushak, N. D.; Matiichuk, V. S.; Ganushchak, N. I. *Russ. J. Org. Chem.* **1998**, *34*, 239–244 (English translation from *Zh. Org. Khim*. **1998**, *34*, 266–271).