Chemistry of Heterocyclic Compounds, Vol. 46, No. 4, 2010

SYNTHESIS OF HETEROCYCLES ON THE BASIS OF PRODUCTS OF ARYLATION OF UNSATURATED COMPOUNDS 22.* 3-ARYL-2-CHLOROPROPANAL IN THE SYNTHESIS OF N-ARYL-5-(R-BENZYL)-1,3-THIAZOLE-2-AMINES

V. S. Matiychuk, N. D.Obushak[1], N. I. Pidlypnyi[1], Yu. V. Ostapiuk[1], and R. M. Voloshchuk[1]**

3-Aryl-2-chloropropanal was obtained by the reaction of arenediazonium chlorides with acrolein in the presence of copper(II) chloride. N-Aryl(2-pyridyl)-5-(R-benzyl)-1,3-thiazole-2-amines were formed in high yield by the reaction of these aldehydes with aryl- and 2-pyridylthioureas. The same compounds were obtained by the reaction of 5-(R-benzyl)-1,3-thiazole-2-amines with aniline.

Keywords: 2-aminothiazoles, arylthioureas, derivatives of thiazole, α-chloro aldehydes, arylation, the Meerwein reaction.

Derivatives of 2-aminothiazole cover a wide spectrum of biological activity [2-8] and are also used in various fields of technology [9, 10]. One of the most suitable methods for the synthesis of 2-aminothiazole is the interaction of α-halocarbonyl compounds with thioamides and thioureas [11-13]. 5-Substituted 2-aminothiazoles have been obtained by this method, using α-halo aldehydes, the range of which is limited. The development of a preparative method for the synthesis of 3-aryl-2-chloropropanal [14,15] provided the possibility to easily obtain 2-amino-5-(R-benzyl)thiazoles.

In this paper a method is proposed for the synthesis of N-aryl-5-(R-benzyl)-1,3-thiazole-2-amines **5a-o** by the interaction of chloro aldehydes **3a-f** with arylthioureas **4a-e** and N-(2-pyridyl)thioureas **4f,g**. The aldehyde starting materials **3a-e** were obtained by chloroarylation of acrolein **1** with the aryldiazonium salts **2a-e**. We note that compounds **3** can also be obtained from 3-arylpropanols which, in their turn, were synthesized from the corresponding cinnamic acids [16]. However this method is preparatively less suitable and the overall yields of the aldehydes **3** are not large.

It was established that cyclization of the chloro aldehydes **3a-e** with arylthioureas **4** occurs on boiling in ethanol, and the presence of bases is not required (method A).

2-Chloro-3-(1-naphthyl)propanal **3f**, prepared by the interaction of naphthyldiazonium tetrachlorocuprate (**2f**) with acrolein **1** [8, 14], was used in the synthesis of compounds **5n,o**.

---

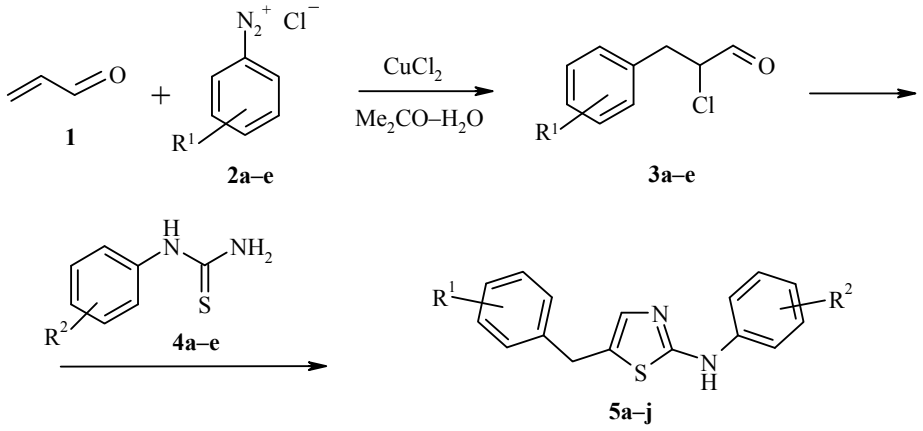
* For Communication 21, see [1].

** To whom correspondence should be addressed, e-mail: obushak@in.lviv.ua.

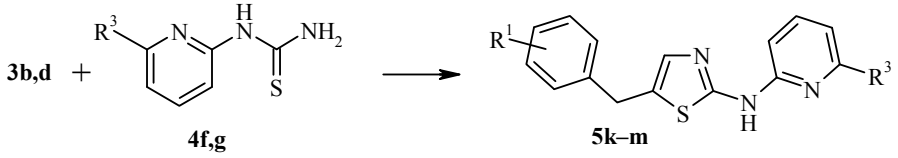
[1]Ivan Franko Lviv National University, Lviv 79005, Ukraine.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No.4, 624-629, April 2010. Original article submitted May 28, 2009.

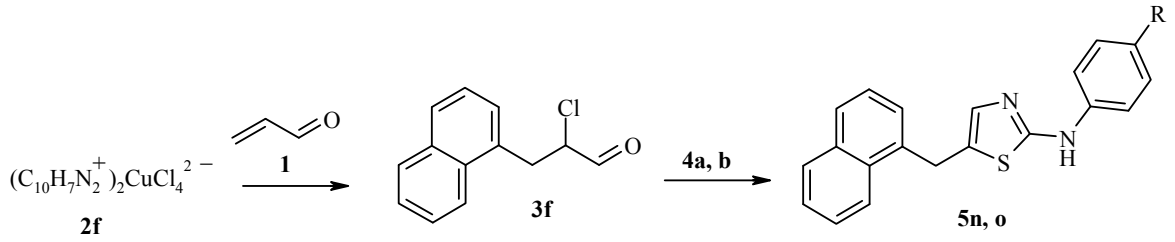
The interaction of the chloro aldehydes **3** with aryl thioureas **4** occurred selectively in all cases: The thiazole ring was formed with the more nucleophilic nitrogen atom. Isomeric 3-aryl-5-(R-benzyl)-2-iminothiazoles were not observed in the reaction mixture. Compounds **5a-o** are readily soluble in polar solvents, insoluble in mineral acids, and form salts with difficulty.



2, 3 a R^1 = 4-Cl, **b** R^1 = 2,3-Cl_2, **c** R^1 = 3,4-Cl_2, **d** R1 = 2-Me, e R^1 = 3-NO_2; 4 **a** R^2 = H, **b** R^2 = 4-Cl, **c** R^2 = 4-Me, **d** R^2 = 3-Me, **e** R^2 = 4-MeO; **5a–c** R^2 = H, **a** R^1 = 4-Cl, **b** R^1 = 2,3-Cl_2, **c** R^1 = 3,4-Cl_2; **d–g** R^2 = 4-Cl, **d** R^1 = 4-Cl, **e** R^1 = 2,3-Cl_2, **f** R^1 = 3,4-Cl_2, **g** R^1 = 2-Me; **h** R^1 = 2,3-Cl_2, R^2 = 4-Me; **i** R^1 = 3-NO_2, R^2 = 3-Me; **j** R^1 = 2-Me, R^2 = 4-OMe

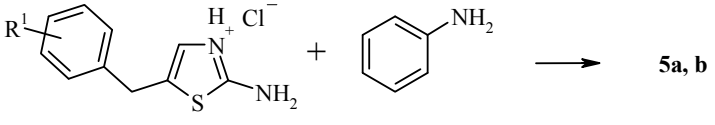


4 f R^3 = H, **g** R^3 = Me; **5 k, l** R^3 = H, **k** R^1 = 2-Me, **l** R^1 = 2,3-Cl_2; **m** R^1 = 2-Me, R^3 = Me



5 n R = H , **o** R = Cl

The structures of compounds **5** were confirmed by ^{1}H NMR spectroscopic data and by directed synthesis, starting from 5-(R-benzyl)-1,3-thiazole-2-amine hydrochlorides **6a,b** and aniline (method B):

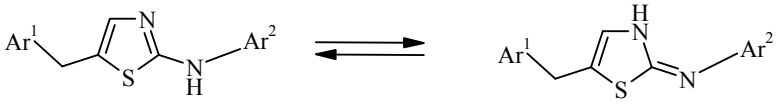


6 a R^1 = 4-Cl, **b** R^1 = 2,3-Cl_2

Table 1. Characteristics of Compounds **5a-o**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
5a	$C_{16}H_{13}ClN_2S$	63.61 / 63.89	4.24 / 4.36	9.04 / 9.31	130-132	50
5b	$C_{16}H_{12}Cl_2N_2S$	57.05 / 57.32	3.44 / 3.61	8.20 / 8.36	194-195	61
5c	$C_{16}H_{12}Cl_2N_2S$	57.03 / 57.32	3.42 / 3.61	8.20 / 8.36	117-118	49
5d	$C_{16}H_{12}Cl_2N_2S$	57.07 / 57.32	3.43 / 3.61	8.21 / 8.36	145-148	52
5e	$C_{16}H_{11}Cl_3N_2S$	51.67 / 51.98	2.79 / 3.00	7.42 / 7.58	185-187	71
5f	$C_{16}H_{11}Cl_3N_2S$	51.62 / 51.98	2.79 / 3.00	7.31 / 7.58	192-193	64
5g	$C_{17}H_{15}ClN_2S$	64.72 / 64.85	4.63 / 4.80	8.78 / 8.90	158	61
5h	$C_{17}H_{14}Cl_2N_2S$	58.24 / 58.46	3.92 / 4.04	8.28 / 8.02	155-156	54
5i	$C_{17}H_{15}N_3O_2S$	62.65 / 62.75	4.57 / 4.65	12.83 / 12.91	184-185	52
5j	$C_{18}H_{18}N_2OS$	69.42 / 69.65	5.42 / 5.84	8.80 / 9.02	122	49
5k	$C_{16}H_{15}N_3S$	68.03 / 68.30	5.21 / 5.37	14.77 / 14.93	172	69
5l	$C_{15}H_{11}Cl_2N_3S$	53.40 / 53.58	3.13 / 3.30	12.36 / 12.50	227	73
5m	$C_{17}H_{17}N_3S$	68.97 / 69.12	5.68 / 5.80	14.04 / 14.22	195	67
5n	$C_{20}H_{16}N_2S$	75.55 / 75.92	5.02 / 5.10	9.02 / 8.85	155	42
5o	$C_{20}H_{15}ClN_2S$	68.06 / 68.46	4.17 / 4.31	7.81 / 7.98	153	45

It should be noted that amino-imino tautomerism is possible for compounds **5** in solution [17, 20]:



Evidently tautomeric conversion occurs rapidly in solution as a result of which broadening of the NH signal is observed in the ^{1}H NMR spectrum. To judge by the chemical shift and the form of the signal (a singlet), equilibrium is shifted to the side of the amino form.

EXPERIMENTAL

^{1}H NMR Spectra of compounds **5a,e,g,i-o** were recorded on a Varian Mercury (400 MHz) instrument, compounds **5b-d,f, h** on a Bruker WP-200 (200 MHz) in DMSO-d_6 (**5a,e,i,n,o**), deuteroacetone (**5b-d,f,h)**, or $CDCl_3$ (**5g, j-m)** with TMS as internal standard. Compounds **6a,b** were obtained by a known method [15].

N-Aryl(2-pyridyl)-5-(R-benzyl)-1,3-thiazole-2-amines 5a-o. A. A solution of the corresponding arylthiourea **4** (10 mmol) and the aldehyde **3** (10 mmol) in ethanol (10 ml) was boiled for 3 h. The residue was decanted, suspended in boiling water and made alkaline with ammonia. It was filtered off and recrystallized from DMF.

Table 2. ^{1}H NMR Spectra of Compounds **5a-o**

Com-pound	Chenical shifts, δ, ppm (*J*, Hz)
5a	4.02 (2H, s, CH_2); 6.91 (1H, t, *J* = 7.2, H-4 C_6H_5); 7.03 (1H, s, thiazole); 7.24-7.30 (4H, m, Ar); 7.37 (2H, d, *J* = 8.1, H-3,5 C_6H_4); 7.56 (2H, d, *J* = 7.8, H-2,6 C_6H_5); 9.99 (1H, s, NH)
5b	4.10 (2H, s, CH_2); 7.10 (1H, s, thiazole); 7.20-7.72 (8H, m, Ar); 9.50 (1H, s, NH)
5c	4.09 (2H, s, CH_2); 6.95 (1H, t, *J* = 7.2, H-4 C_6H_5); 7.10 (1H, s, thiazole); 7.20-7.70 (7H, m, Ar); 9.40 (1H, s, NH)
5d	4.03 (2H, s, CH_2); 7.06 (1H, s, thiazole); 7.28 (2H, d, *J* = 8.8, H-3,5 C_6H_4NH); 7.32 (2H, d, *J* = 8.4, H-2,6 C_6H_4); 7.37 (2H, d, *J* = 8.4, H-3,5 C_6H_4); 7.62 (2H, d, *J* = 8.8, H-2,6 C_6H_4NH); 10.16 (1H, s, NH)
5e	4.23 (2H, s, CH_2); 7.09 (1H, s, thiazole); 7.25-7.73 (7H, m, Ar); 9.45 (1H, s, NH)
5f	4.10 (2H, s, CH_2); 7.10 (1H, s, thiazole); 7.25-7.58 (5H, m, Ar); 7.72 (2H, d, *J* = 8.7, H-2,6 C_6H_4); 9.22 (1H, s, NH)
5g	2.30 (3H, s, CH_3); 4.01 (2H, s, CH_2); 6.97 (1H, s, thiazole); 7.11-7.22 (4H, m, C_6H_4); 7.31 (2H, d, *J* = 8.8, H-3,5 C_6H_4NH); 7.61 (2H, d, *J* = 8.8, H-2,6 C_6H_4NH); 10.11 (1H, s, NH)
5h	2.23 (3H, s, CH_3); 4.09 (2H, s, CH_2); 6.70-7.58 (8H, m, thiazole + Ar); 9.40 (1H, br. s, NH)
5i	2.27 (3H, s, CH_3); 4.26 (2H, s, CH_2); 7.11 (1H, s, thiazole); 6.90- 7.17 (4H, m, C_6H_4NH); 7.65 (1H, t, *J* = 7.6, H-5 C_6H_4); 7.83 (1H, d, *J* = 7.6, H-6 C_6H_4); 8.13 (1H, dd, ^4J = 2.1, ^3J = 8.0, H-4 C_6H_4); 8.23 (1H, br. s, H-2 C_6H_4); 9.81 (1H, s, NH)
5j	2.29 (3H, s, CH_3); 3.71 (3H, s, OCH_3); 3.98 (2H, s, CH_2); 6.86-6.89 (3H, m, thiazole + Ar); 7.13-7.20 (4H, m, Ar); 7.47 (2H, d, *J* = 8.8, Ar); 9.72 (1H, s, NH)
5k	2.30 (3H, s, CH_3); 4.05 (2H, s, CH_2); 6.84-6.89 (1H, m, H-5 Py); 7.00-7.04 (1H, m, H-3 Py); 7.06 (1H, s, thiazole); 7.12-7.24 (4H, m, C_6H_4); 7.63-7.67 (1H, m, H-4 Py); 8.20-8.23 (1H, m, H-6 Py); 11.03 (1H, s, NH)
5l	4.23 (2H, s, CH_2); 6.85-6.90 (1H, m, H-5 Py); 7.02-7.06 (1H, m, H-3 Py); 7.12 (1H, s, thiazole); 7.30-7.71 (4H, m, C_6H_3 + H-4 Py); 8.23-8.26 (1H, m, H-6 Py); 11.11 (1H, s, NH)
5m	2.32 (3H, s, CH_3); 2.39 (3H, s, CH_3); 4.04 (2H, s, CH_2); 6.73 (1H, d, *J* = 7.6, H-5 Py); 6.83 (1H, d, *J* = 7.8, H-3 Py); 7.00 (1H, s, thiazole); 7.11-7.21 (4H, m, C_6H_4); 7.54 (1H, t, *J* = 7.8, H-4 Py); 10.96 (1H, s, NH)
5n	4.41 (2H, s, CH_2); 6.79 (1H, t, *J* = 7.8, H-4 C_6H_5); 6.85 (1H, s, thiazole); 7.14 (2H, t, *J* = 7.8, H-3,5 C_6H_5); 7.36-7.50 (6H, m, Ar); 7.70-7.74 (1H, m, $C_{10}H_7$); 7.82 (1H, d, *J* = 7.4, $C_{10}H_7$); 8.07 (1H, d, *J* = 7.4, $C_{10}H_7$); 9.68 (1H, s, NH)
5o	4.41 (2H, s, CH_2); 6.85 (1H, s, thiazole); 7.12 (2H, d, *J* = 8.2, H-3,5 C_6H_4); 7.35-7.50 (4H, m, $C_{10}H_7$); 7.53 (2H, d, *J* = 8.2, H-2,6 C_6H_4); 7.71-7.75 (1H, m, $C_{10}H_7$); 7.83 (1H, d, *J* = 7.3, $C_{10}H_7$); 8.05 (1H, d, *J* = 7.3, $C_{10}H_7$); 9.83 (1H, s, NH)

B. Equimolar mixtures of the hydrochlorides **6a,b** and aniline were heated at 180-200°C. After cooling, the oily residue was treated successively with hot water and alcohol and recrystallized from DMF. The yields of compounds **5a** and **5b** were 24 and 20% respectively.

REFERENCES

1. M. D. Obushak, V. S. Matiychuk, and V. V. Turytsa, *Tetrahedron Lett.,* **50,** 6112 (2009).
2. S. Ueda, H. Terauchi, M. Kawasaki, A. Yano, and M. Ido, *Chem. Pharm. Bull.,* **52**, 634 (2004).

3. D. Zuev, J. A. Michne, S. S. Pin, J. Zhang, M. T. Taber, and G. M. Dubowchik, *Bioorg. Med. Chem. Lett.,* **15**, 431 (2005).
4. A. Dondoni and A. Marra, *Chem. Rev.,***104**, 2557 (2004).
5. R. M. Borzilleri, R. S. Bhide, J. C. Barrish, C. J. D'Arienzo, G. M. Derbin, J. Fargnoli, J. T. Hunt, R. Jeyaseelan, A. Kamath, D. W. Kukral, P. Marathe, S. Mortillo, L. Qian, J. S. Tokarski, B. S. Wautlet, X. Zheng, and L. J. Lombardo, *J. Med. Chem.,* **49**, 3766 (2006).
6. Y. Sagara, M. Mitsuya, M. Uchiyama, Y. Ogino, T. Kimura, N. Ohtake, and T. Mase, *Chem. Pharm. Bull.,* **53**, 437 (2005).
7. S. Wang, C. Meades, G. Wood, A. Osnowski, S. Anderson, R. Yuill, M. Thomas, M. Mezna, W. Jackson, C. Midgley, G. Griffiths, J. Fleming, S. Green, I. McNae, S.-Y. Wu, C. McInnes, D. Zheleva, M. D. Walkinshaw, and P. M. Fischer, *J. Med. Chem.,***47**, 1662 (2004).
8. B. S. Zimenkovskii, R. V. Kutsyk, R. B. Lesyk, V. S. Matiychuk, N. D. Obushak, and T. I. Klofinskaya, *Khim.-Farm. Zh.,* **40**, No.6, 57 (2006).
9. J. V. Metzger (editor), *Thiazole and Its Derivatives.* John Wiley and Sons, London (1979), Vol. 3, p.23.
10. A. R. Katritzky, C. W. Rees, and E. F. V. Scriven (editors), *Comprehensive Heterocyclic Chemistry,* Elsevier (1997), Vol. 6, p. 326.
11. I. K. Moiseev, M. N. Zemtsova, and N. V. Makarova, *Khim. Geterotsikl, Soed.,* 867 (1994). [*Chem. Heterocycl. Comp.,* **30**, 745 (1994)].
12. J. V. Metzger (editor), *Thiazole and Its Derivatives.* John Wiley and Sons, London (1979), Vol. 1, p. 165.
13. J. M. Sprague and A. H. Land, in: R. Elderfield (editor), *Heterocyclic Compounds* (Russian translation). Izd-vo inostr. lit., Moscow (1961), Vol. 5, p.395.
14. N. D. Obushak, V. S. Matiichuk, and N. I. Ganushchak, *Zh. Org. Khim.,* **33**, 1081 (1997).
15. N. D. Obushak, V. S. Matiichuk, R. Ya. Vasyl'shin, and Yu. V. Ostashok, *Zh. Org. Khim.,* **40**, 412 (2004).
16. D. S. Emolat'ev, V. L. Alifanov, V. B. Rybakov, E. V. Babaev, and E. V. Van der Eycken, *Synthesis*, 2083 (2008).
17. A. P. Engoyan, K. A. Eliazyan, V. A. Pivazyan, E. A. Kazaryan, and V. V. Dovlatyan, *Khim. Geterotsikl. Soedin.,* 1240 (2005). [*Chem. Heterocycl. Comp.,* **41**, 1062 (2005)].
18. M. Annese, A. B. Corradi, L. Forlani, C. Rizzoli, and P. Sgarabotto, *J. Chem. Soc., Perkin Trans 2,* 615 (1994).
19. T. N. Birkinshaw, S. A. Harkin, P. T. Kaye, G. D. Meakins, and A. K. Smith, *J. Chem. Soc., Perkin Trans 1,* 939 (1982).
20. G. C. Barrett, *Tetrahedron*, **36**, 2023 (1980).