NOVEL Cu-CATALYZED METHODS FOR THE SYNTHESIS OF FUSED THIAZOLES USING *S*,*N*-DIARYLATION REACTION

Keywords: imidazo[2,1-*b*]thiazoles, copper catalysis, phase transfer catalysis.

Imidazothiazoles and related compounds are of great interest as biologically active compounds [1–6]. Imidazo[2,1-*b*]benzothiazole and its benzo analogs have been usually obtained from 2-aminobenzothiazole in the system chloroacetaldehyde/1-butanol [7], from 1-(3-chlorophenyl)-2-mercaptoimidazole in $NaNH_2/NH_3$ [8], from 2-iodobenzothiazole and 2-iodoaniline in CuI/1,10-phenanthroline/Cs_2CO_3/xylene [9], from 2-mercaptobenzimidazole and 1-bromo-5-nitrophthalonitrile with K_2CO_3 [10], or by photolysis of 1-(2-benzothiazolyl)benzotriazole [11]. However, there is no simple and general procedure for the synthesis of benzo-fused imidazo[2,1-*b*]thiazoles and thiazolo[3,2-*b*][1,2,4]triazoles. We have elaborated novel and simple Cu-catalyzed method for the preparation of these heterocyclic systems. Besides, such Cu-catalyzed synthesis of new thiazole ring by stepwise tandem *S*- and *N*-arylation reactions of substrates of type **1–3** is described for the first time.

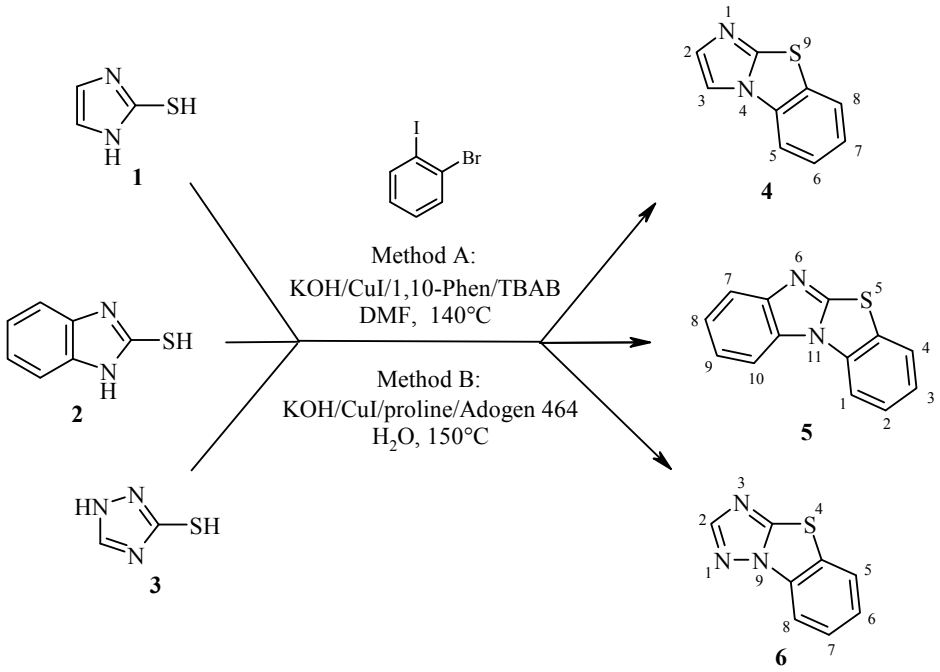
The high activity of copper(I) catalysts in *N*-arylation of imidazole and related heterocycles was recently demonstrated [12–17]. Concurrently, the combination of

alkali bases with tetrabutylammonium bromide (TBAB) as phase transfer catalyst was presented in some recent articles [18, 19].

Synthesis of thiazoles **4** and **5** were carried out from corresponding thiols **1** and **2** by one-pot stepwise *S*,*N*-diarylation reaction with 1-bromo-2-iodobenzene in the bicatalytic system solid KOH/CuI/1,10-phen/TBAB/DMF (Scheme, Method A).

Similarly [1,2,4]triazolo[5,1-*b*][1,3]benzothiazole (**6**) was prepared from 3-mercaptotriazole **3** and 1-bromo-2-iodobenzene.

We have likewise developed a novel catalytic system for the preparation of fused thiazoles **4**–**6** in the water. Thus, interaction of compound **2** with 1-bromo-2-iodobenzene in the system KOH/CuI/proline/Adogen 464 (100 mg)/ H_2O leads to desired product **5** in 74% yield (Scheme, Method B). Adogen 464 (methyl-trialkylammonium chloride) as a phase transfer agent or cationic surfactant has been widely used in organic synthesis [20]. However, the use of Adogen 464 as an additive in Cu-catalyzed reactions in water was demonstrated for the first time. Interestingly, that in the absence of Adogen 464 only trace amounts of product **5** was obtained. Moreover, workup of reaction mixture in the case of compound **5** is very simple – the product was isolated by filtration, followed by recrystallyzation from hexane–EtOAc mixture to get an analytical sample. Synthesis of compounds **4** and **6** from thiols **1** and **3** using Method B was less effective.



In summary, a simple one flask method for the selective preparation of benzo-fused imidazo[2,1-*b*]thiazoles and [1,2,4]triazolo[5,1-*b*][1,3]benzothiazole from corresponding thiols and 1-bromo-2-iodobenzene in the system solid KOH/CuI/ 1,10-phen/TBAB/DMF by *S*,*N*-tandem arylation reactions has been developed.

^{1}H And ^{13}C NMR spectra were registered on Varian Mercury BB spectrometer (400 and 100 MHz, respectively) in $CDCl_3$. Internal standard – solvent signal (δ 7.25 and 77.0 ppm, respectively). HRMS spectra were recorded on Micromass Q-TOF Micro quadrupole time-of-flight high resolution mass spectrometer. Leucine enkephalin was used as internal lock mass for accurate mass calculation. Melting points were detected on Boetius apparatus

equipped with visual detector PHMH 05. Thiols **1**–**3**, 1-bromo-2-iodobenzene (all Acros), CuI, Bu_4NBr, 1,10-phenanthroline (Reahim) and dimethylformamide (extra dry, over molecular sieves, Acros) were used without purification.

Synthesis of fused thiazoles 4–6 (General Method). A. Solid KOH (0.39 g, 6.0 mmol) was added to the solution of an appropriate thiol **1**–**3** (1.5 mmol), 1-bromo-2-iodobenzene (0.42 g, 1.5 mmol), CuI (0.057 g, 0.3 mmol), 1,10-phenanthroline (0.05 g, 0.3 mmol) and TBAB (0.097 g, 0.3 mmol) in dry DMF (10 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at 140°C for 18 h (products **4** and **5**) or 48 h (product **6**) under argon. The solvent was removed under reduced pressure and the crude residue was chromatographed on silica using hexane–EtOAc, 4:1 to 0:1, as eluent.

B. Solid KOH (0.22 g, 4.0 mmol) was added to the solution of an appropriate thiol **1**–**3** (1.0 mmol) and 1-bromo-2-iodobenzene (0.340 g, 1.2 mmol), CuI (0.038 g, 0.2 mmol), proline (0.020 g, 0.2 mmol), and Adogen 464 (100 mg) in water (2 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at 150 °C (TLC-control) for 18 h under argon. The products was removed by filtration (for compound **5**) or extracted with CH_2Cl_2 (for compounds **4** and **6**). The extract of compounds **4** and **6** was dried over Na_2SO_4, concentrated under reduced pressure, and the crude residue was chromatographed on silica using hexane – ethyl acetate (from 4:1 to 0:1) as eluent.

Imidazo[2,1-*b*][1,3]benzothiazole (4) [21]. Yield 29% (Method A); traces (Method B). Oil.

Benzimidazo[2,1-*b*][1,3]benzothiazole (5) [11]. Yield 59% (Method A); 74% (Method B). Mp 118–120°C.

[1,2,4]Triazolo[5,1-*b*][1,3]benzothiazole (**6**). Yield 14% (Method A); 7% (Method B). Mp 73–74°C. ^{1}H NMR, δ, ppm (*J*, Hz): 7.43 (1H, t, *J* = 8.0) and 7.54 (1H, t, *J* = 8.0, H-6,7); 7.77 (1H, d, *J* = 7.6) and 7.97 (1H, d, *J* = 7.6, H-5,8); 8.21 (1H, s, H-2). ^{13}C NMR spectrum, δ, ppm: 113.5; 124.5; 125.9; 127.0; 129.7 (C-4a); 131.4 (C-8a); 155.7 (C-3a); 156.1 (C-2). Found, *m/z* (ESI): 176.0296 [M+H]. $C_8H_6N_3S$. Calculated, *m/z*: 176.0282.

R E F E R E N C E S

1. A. Chimirri, S. Grasso, G. Romeo, M. Zappala, *Heterocycles*, **27**, 1975 (1988).
2. K. A. Al-Rashood, H. A. Abdel-Aziz, *Molecules*, **15**, 3775 (2010).
3. Э. Абеле, Р. Абеле, П. Арсенян, С. Беляков, М. Веверис, Э. Лукевиц, *ХГС,* 274 (2007). [*Chem. Heterocycl. Compd.*, **43**, 220 (2007).]
4. R. Ābele, P. Arsenyan, M. Vēveris, E. Ābele, *Heterocycl. Commun.*, **16**, 9 (2010).
5. N. Scheinfeld, J. D. Rosenberg, J. M. Weinberg, *Am. J. Clin. Dermatol*., **5**, 97 (2004).
6. C. B. Vu, J. E. Bemis, J. S. Disch, P. Y. Ng, J. J. Nunes, J. C. Milne, D. P. Carney, A. V. Lynch, J. J. Smith, S. Lavu, P. D. Lambert, D. J. Gagne, M. R. Jirousek, S. Schenk, J. M. Olefsky, R. B. Perni, *J. Med. Chem.*, **52**, 1275 (2009).
7. T. Seki, S. Tasaka, R. Hoshino, US Pat. Appl. 4968708.
8. H. Ogura, T. Itoh, *Chem. Pharm. Bull*., **18**, 1981 (1970).
9. Z. Wu, Q. Huang, X. Zhou, L. Yu, Z. Li, D. Wu, *Eur J. Org. Chem.*, 5242 (2011).
10. И. Г. Абрамов, А. В. Смирнов, М. Б. Абрамова, С. А. Ивановский, В. В. Плахтинский, *ХГС*, 1219 (2000). [*Chem. Heterocycl. Compd.*, **36**, 1062 (2000).]
11. D. C. K. Lin, D. C. De Jongh, *J. Org. Chem.*, **39**, 1780 (1974).
12. J.-B. Lan, L. Chen, X.-Q. Yu, J.-S. You, R.-G. Xie, *Chem. Commun*., 188 (2004).
13. X. Lv, W. Bao, *J. Org. Chem*., **72**, 3863 (2007).
14. L. Xu, D. Zhu, F. Wu, R. Wang, B. Wan, *Tetrahedron*, **61**, 6553 (2005).
15. H.-J. Cristau, P. P. Cellier, J.-F. Spindler, M. Taillefer, *Chem.–Eur. J*., **10**, 5607 (2004).
16. R. A. Altman, S. L. Buchwald, *Org. Lett*., **8**, 2779 (2006).
17. Y.-Z. Huang, J. Gao, H. Ma, H. Miao, J. Xu, *Tetrahedron Lett*., **49**, 948 (2008).

18. J. W. W. Chang, X. Xu, P. W. H. Chan, *Tetrahedron Lett*., **48**, 245 (2007).
19. J. R. Naber, S. L. Buchwald, *Angew. Chem.*, *Int. Ed.*, **49**, 9469 (2010).
20. E. V. Dehmlow, S. S. Dehmlow, *Phase Transfer Catalysis*, Verlag Chemie, Weinheim, 1983, 2nd ed.
21. M. Huys-Francotte, H. Balli, *Helv. Chim. Acta,* **73**, 1679 (1990).

T. Beresneva[1], J. Popelis[1], E. Abele[1]*

[1] *Latvian Institute of Organic Synthesis*,
21 Aizkraukles St., *Riga LV-1006*, *Latvia*
e-mail: abele@osi.lv

Received 29.03.2012
In revised version 12.02.2013

ХГС. – 2013. – №. 2. – С. 370