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Synthesis and antibacterial activity of hydroxylated 2-arylbenzothiazole derivatives

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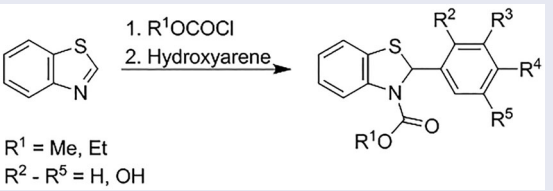
ABSTRACT

N-acyliminium reagents formed *in situ* from benzothiazole and alkyl chloroformates react with hydroxyarenes in a Friedel-Crafts manner, providing access to 2-(hydroxyaryl)-benzothiazolines with antibacterial properties.

GRAPHICAL ABSTRACT



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2-arylbenzothiazoles; phenols; naphthols; amidoalkylation; antibacterial activity

Introduction

The 2-arylbenzothiazole moiety is present in many biologically active compounds and medicines.[1] Hydroxylated 2-phenylbenzothiazoles in particular are interesting as cytotoxic agents[2] and calcium antagonists.[3] In recent years their successful application as CN-sensors,[4] photosensitizers,[5] immunomodulators,[6] β-glucuronidase inhibitors[7] and DNA binders[8] has also been reported. The most common use of 2-hydroxyphenyl (or naphthyl) benzothiazoles is as fluorescent probes[9–19] due to their excited-state intramolecular proton transfer (ESIPT) based emission possibility and large Stokes shifts. Because of this wide spectrum of possible applications, 2-substituted benzothiazoles have attracted considerable attention from the synthetic community.[20] The mainly employed method for the preparation of 2-arylbenzothiazoles is based on the cyclocondensation of *o*-aminothiophenol with aromatic aldehydes[21–23] or carboxylic acids.[24] Other approaches involve cyclization reactions of bis-(2-benzalaminophenyl)disulfides,[25,26] thiophenolic schiff bases[27] or thiobenzanilides.[28] This heterocyclic

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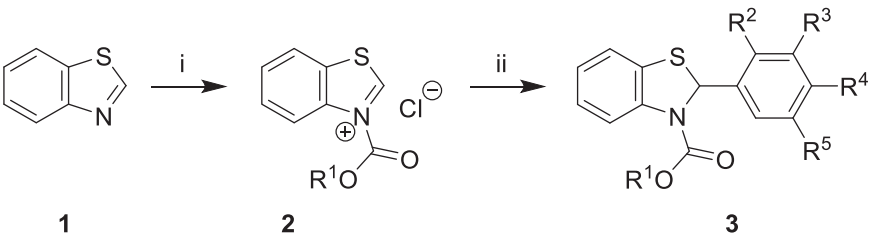
system has also been accessed via reactions of *o*-chloronitrobenzenes or *o*-iodoanilines with various cyclization agents[29–31] and arylmethyl thiols with *o*-substituted amines.[32] Less popular synthetic routes include annulation of anilines with ethers,[33] azolylation of heteroarenes[34] and hydroxylation of heteroaryl halides.[35] Methods of direct arylation of benzothiazole[36,37] and cross-coupling of heteroaryl thiols with arylzinc reagents[38] have also been investigated.

Although the variety of known reactions leading to 2-substituted benzothiazoles is significant, many of them are limited with regard to functional group tolerance and/or availability of reagents and catalysts. Such limitations are particularly relevant to the synthesis of hydroxylated 2-arylbenzothiazoles, and for this reason we chose to investigate an approach for alkylative coupling of the benzothiazole ring to the aromatic rings of various phenols and naphthols. This approach relies on the initial conversion of the thiazole ring to a N-acyliminium species, which is sufficiently electrophilic to further react in a Friedel-Crafts manner with activated aromatic nucleophiles. Combined with a subsequent oxidative rearomatization, this approach has previously been very useful to us in the synthesis 2-heteroaryl substituted thiazoles, such as the natural product *Camalexin* and related analogues.[39,40] Additional interest in the hydroxyarene-coupled benzothiazoles is based on analogy with some antibacterial and cytotoxic compounds.[41,42]

Results and discussion

The N-acyliminim reagents **2** were prepared simply by adding methyl or ethyl chloroformate to a solution of benzothiazole in acetonitrile and were used immediately in reactions with activated aromatic substrates. We studied the reactivity of **2** toward five different phenols – phenol, pyrocatechol, pyrogallol, resorcinol and hydroquinone (Scheme 1, Table 1). In the initial experiments all hydroxyarenes were successfully amidoalkylated in the aromatic ring for 1 to 6 h at reflux temperature, but in nearly all cases except for phenol these conditions led to formation of positional isomers and overalkylation. The best yields of mono amidoalkylated products **3** were obtained when the N-acyliminium agent was taken in twofold excess and the reaction mixtures were allowed to stand at 20 °C for two to three days (**3a–d**, **3i–j**) or at 0 °C for 3 to 5 h (**3e–h**). Under these conditions only pyrogallol gave minor amount (10%) of dialkylated products.

The amidoalkylation was also tried with a set of three naphthols (Table 2). Here the reactions proceeded better with no excess of the N-acyliminium reagent. The

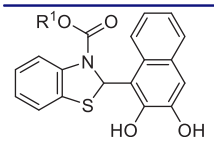
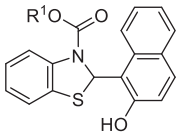
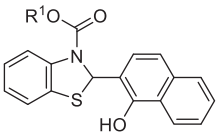


Scheme 1. Amidoalkylative coupling of benzothiazole and hydroxyarenes. Reagents and conditions: (i) 1–1.5 equiv. R^1OCOCl in CH_3CN; (ii) Hydroxyarene. See Table 1 for temperature and duration.

Table 1. Products obtained from the corresponding phenols according to Scheme 1.

3	R^1	R^2	R^3	R^4	R^5	T (°C)	Time (h)	Yield (%)
a	Et	H	H	OH	H	20	80	83
b	Me	H	H	OH	H	20	80	75
c	Et	H	OH	OH	H	20	80	94
d	Me	H	OH	OH	H	20	80	91
e	Et	OH	OH	OH	H	0	5	60
f	Me	OH	OH	OH	H	0	5	68
g	Et	OH	H	OH	H	0	3	52
h	Me	OH	H	OH	H	0	3	65
i	Et	OH	H	H	OH	20	50	75
j	Me	OH	H	H	OH	20	50	55

Table 2. Products obtained from the corresponding naphthols and acyliminium reagents **2** in acetonitrile at 20 °C.

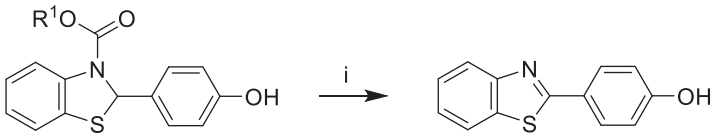
Product		R^1	Time (h)	Yield (%)
	**4a**	Me	50	60
	4b	Et	50	40
	**5a**	Me	80	97
	5b	Et	80	80
	**6a**	Me	24	72
	6b	Et	24	53

amidoalkylated products **4a**, **b**–**6a**, **b** were obtained in 40−97% yield at 20 °C, with reaction durations indicated in Table 2.

After the successful amidoalkylative coupling of benzothiazole with hydroxyaryl substrates, we experimented with oxidative rearomatization of the benzothiazoline ring in the obtained products **3**−**6**. In the 2-(hydroxyphenyl) series **3** these experiments led to complex mixtures of oxidized products and failed to provide access to the desired benzothiazole derivatives. An exception was the pair **3a**, **b** – both compounds were cleanly converted to the known[23,35] product **7** upon oxidation with *o*-chloranil at 20 °C in acetonitrile (Scheme 2).

In the 2-(hydroxynaphthyl) series **4**−**6**, under the same conditions, only the oxidation of beta-naphthol derivatives **5a**, **b** proceeded cleanly and with good yields. However, the spectral characteristics of the obtained products **8** indicated that their structure is of quinone methide type rather than aromatic (Scheme 3).

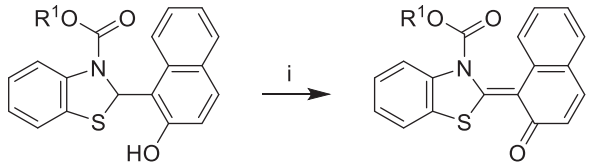
The newly synthesized benzothiazoline derivatives **3**−**7** were screened for antibacterial activity against two Gram-positive strains (*Staphylococcus aureus* ATCC 6538 P and *Bacillus licheniformis* ATCC 14580) and one Gram-negative strain (*Escherichia coli* ATCC 8739), using the hole plate method in Mueller-Hinton agar with 100 µL loading of 1 mg/mL solutions in DMSO-Water (1:1 vol.). Inhibition of bacterial growth was



3a, R^1 = Et
3b, R^1 = Me

7 67% from **3a**
72% from **3b**

Scheme 2. Oxidative rearomatization of **3a**, **b** to **7**. Reagents and conditions: (i) o-chloranil, acetonitrile, 20 °C, 2 h.



5a, R^1 = Me
5b, R^1 = Et

8a (91%)
8b (76%)

Scheme 3. Oxidation of beta-naphthol derivatives **5a**, **b**. Reagents and conditions: (i) o-chloranil, acetonitrile, 20 °C, 2 h.

Table 3. Antibacterial activity of the obtained benzothiazole derivatives **3**–**7**.

	S. aureus ATCC 6538P		*B. licheniformis ATCC 14580*	
Compound	Inhibition zone (mm)[a]	MIC (mg/mL)[b]	Inhibition zone (mm)[a]	MIC (mg/mL)[b]
3a	19	0.0063	–	–
3b	13	0.0125	–	–
3c	19	0.0063	17	0.0125
3d	20	0.0063	19	0.0032
3e	17	0.0063	15	0.0063
3f	16	0.0032	14	0.0500
3g	19	0.0063	15	0.0016
3h	16	0.0016	15	0.0250
3i	16	0.0016	16	0.0008
3j	14	0.0063	15	0.0016
4b	15	0.0063	12	0.0125
5a	14	0.0125	–	–
5b	13	0.0032	–	–
6b	13	0.0016	–	–
7	15	0.0063	–	–

[a]Assessed by the hole-plate method with 100 µL loading of 1 mg/mL solutions in 1:1 DMSO-Water.
[b]Ampicillin was used as a positive control with MIC = 0.0004 mg/mL against both strains.

observed only for the Gram-positive strains. Minimal inhibitory concentrations (MIC) were determined for all active compounds with Ampicillin as positive control (Table 3). The selectivity of the tested compounds toward Gram-positive bacteria along with the low MICs observed for some of them (notably the hydroquinone derivative **3i**) provide a good lead for further structure optimization.

A screening was also done against *Candida albicans* and *Saccharomyces serevisiae*, but only three compounds (**3a**, **3b** and **4b**) showed weak activity against these yeasts.

Experimental

General information

All solvents and reagents, such as benzothiazole, phenols, naphthols and alkyl chloroformates were purchased from Sigma-Aldrich or Merck and were used without further purification. Melting points were measured on a Boetius PHMKO5 hot stage apparatus and are uncorrected. IR spectra were measured on VERTEX 70 FT-IR spectrometer (Bruker Optics, Germany). ^{1}H-, ^{13}C-NMR spectra were measured on Bruker Avance AV600 or DRX250 spectrometers and chemical shifts (δ, ppm) are downfield from TMS. The NMR spectra of the amidoalkylated hydroxyaryl derivatives, both phenyl and naphthyl, indicated slow rotameric interconversions with broad coalescent signals at 20 °C, which is most likely due to the presence of tertiary carbamate group. Adequate assignment of peaks and structure determination in most cases became possible only when the spectra were measured at 80 °C in DMSO-d_6, as indicated in the text below. TLC was done on precoated 0.2 mm Merck silica gel 60 plates. Silica gel or neutral alumina were used for column chromatography. Mass spectral measurements were performed on a Thermo Scientific Q Exactive hybrid quadrupole-orbitrap mass spectrometer.

Synthesis of amidoalkylated phenols (3), general procedure

The corresponding alkyl chloroformate (2 mmol) was added dropwise to a magnetically stirred solution of benzothiazole (0.270 g, 2 mmol, 0.22 mL) in acetonitrile (10 mL), followed immediately by the corresponding phenol (1 mmol). The stirring was then continued under the conditions indicated in Table 1. After that, the solvent was evaporated under reduced pressure, the residue was dissolved in dichloromethane (40 mL) and washed twice with water. The organic layer was dried (Na_2SO_4) and the crude mixture was dry-loaded onto silica gel. The products were isolated by column chromatography on silica gel with mixtures of petrol/diethyl ether as the eluent.

Synthesis of amidoalkylated naphthols (4, 5 and 6), general procedure

The corresponding alkyl chloroformate (1.2 mmol) was added dropwise to a magnetically stirred solution of benzothiazole (0.135 g, 1 mmol, 0.11 mL) in acetonitrile (7 mL), followed immediately by the corresponding naphthol (1 mmol). The stirring was then continued at 20 °C for the time indicated in Table 2. The solvent was evaporated under reduced pressure and the crude mixture was dry-loaded onto silica gel. The products were isolated by column chromatography on silica gel with mixtures of petrol/diethyl ether as the eluent.

Oxidation of the amidoalkylated phenols. Synthesis of compounds 7 and 8, general procedure

To the corresponding compound **3** or **5** (0.5 mmol) in acetonitrile (7 mL) was added o-chloranil (0.5 mmol, 0.123 g). The reaction mixture was stirred for 2 h at 20 °C and the solvent was then removed under reduced pressure dry loading the crude mixture onto silica gel. The products were isolated by silica gel column chromatography with petrol – diethyl ether as the eluent.

4-(benzo[d]thiazol-2-yl)phenol **7**: The spectral and melting point data for this compound coincided with the literature.[23,35]

Conclusions

We have demonstrated that the N-acyliminium reagents formed *in situ* from benzothiazole and alkyl chloroformates react with hydroxyarenes in a Friedel-Crafts manner, providing access to 2-(hydroxyaryl)-benzothiazoline derivatives. Although the attempts for oxidative rearomatization of the obtained benzothiazolines have been only partly successful, these compounds have shown encouraging antibacterial properties.

Full experimental details, characterization data and copies of ^{1}H, ^{13}C-NMR spectra for synthesized compounds can be found via the "Supplementary content" section.

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References

[1] Keri, R. S.; Patil, M. R.; Patil, S. A.; Budagumpi, S. A Comprehensive Review in Current Developments of Benzothiazole-based Molecules in Medicinal Chemistry. *Eur. J. Med. Chem.* **2015**, *89*, 207–251. DOI: 10.1016/j.ejmech.2014.10.059.

[2] Stevens, M. F.; McCall, C. J.; Lelieveld, P.; Alexander, P.; Richter, A.; Davies, D. E. Structural Studies on Bioactive Compounds. 23. Synthesis of Polyhydroxylated 2-Phenylbenzothiazoles and a Comparison of Their Cytotoxicities and Pharmacological Properties with Genistein and Quercetin. *J. Med. Chem.* **1994**, *37*, 1689–1695. DOI: 10.1021/jm00037a020.

[3] Yamamoto, K.; Fujita, M.; Tabashi, K.; Kawashima, Y.; Kato, E.; Oya, M.; Iso, T.; Iwao, J. Novel Calcium Antagonists. Synthesis and Structure-Activity Relationship Studies of Benzothiazoline Derivatives. *J. Med. Chem.* **1988**, *31*, 919–930. DOI: 10.1021/jm00400a006.

[4] Tang, L.; Zou, Y.; Zhong, K.; Bian, Y. A Novel Benzothiazole-Based Enaminone as a Fluorescent Probe for Highly Selective and Sensitive Detection of CN. *RSC Adv.* **2016**, *6*, 48351–48356. DOI: 10.1039/C6RA07909A.

[5] Yang, P.; Zhao, J.; Wu, W.; Yu, X.; Liu, Y. Accessing the Long-Lived Triplet Excited States in Bodipy-Conjugated 2-(2-Hydroxyphenyl) Benzothiazole/Benzoxazoles and Applications as Organic Triplet Photosensitizers for Photooxidations. *J. Org. Chem.* **2012**, *77*, 6166–6178. DOI: 10.1021/jo300943t.

[6] Khan, K. M.; Mesaik, M. A.; Abdalla, O. M.; Rahim, F.; Soomro, S.; Halim, S. A.; Mustafa, G.; Ambreen, N.; Khalid, A. S.; Taha, M.; et al. The Immunomodulation Potential of the Synthetic Derivatives of Benzothiazoles: Implications in Immune System Disorders through in Vitro and in Silico Studies. *Bioorg. Chem.* **2016**, *64*, 21–28. DOI: 10.1016/j.bioorg.2015.11.004.

[7] Khan, K. M.; Rahim, F.; Halim, S. A.; Taha, M.; Khan, M.; Perveen, S.; Ul-Haq, Z.; Mesaik, M. A.; Iqbal Choudhary, M. Synthesis of Novel Inhibitors of β-Glucuronidase Based on Benzothiazole Skeleton and Study of Their Binding Affinity by Molecular Docking. *Bioorganic Med. Chem.* **2011**, *19*, 4286–4294. DOI: 10.1016/j.bmc.2011.05.052.

[8] Nagaraju, B.; Kovvuri, J.; Kumar, C. G.; Routhu, S. R.; Shareef, M. A.; Kadagathur, M.; Adiyala, P. R.; Alavala, S.; Nagesh, N.; Kamal, A. Synthesis and Biological Evaluation of Pyrazole Linked Benzothiazole-β-Naphthol Derivatives as Topoisomerase I Inhibitors with DNA Binding Ability. *Bioorg. Med. Chem.* **2019**, *27*, 708–720. DOI: 10.1016/j.bmc.2019.01.011.

[9] Satam, M. A.; Telore, R. D.; Tathe, A. B.; Gupta, V. D.; Sekar, N. A Combined Theoretical and Experimental Investigation on the Solvatochromism of ESIPT3-(1,3-Benzothiazol-2-yl)-2-Hydroxynaphthalene-1-Carbaldehyde. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **2014**, *127*, 16–24. DOI: 10.1016/j.saa.2014.01.120.

[10] Tang, L.; He, P.; Zhong, K.; Hou, S.; Bian, Y. A New Hydroxynaphthyl Benzothiazole Derived Fluorescent Probe for Highly Selective and Sensitive Cu(2+) detection. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **2016**, *169*, 246–251. DOI: 10.1016/j.saa.2016.06.045.

[11] Liao, Y.-X.; Wang, M.-D.; Li, K.; Yang, Z.-X.; Hou, J.-T.; Wu, M.-Y.; Liu, Y.-H.; Yu, X.-Q. A Highly Sensitive and Selective "Turn-on" Fluorescent Probe for Hypochlorous Acid Monitoring. *RSC Adv.* **2015**, *5*, 18275–18278. DOI: 10.1039/C4RA14579H.

[12] Goswami, S.; Das, A. K.; Manna, A.; Maity, A. K.; Fun, H.-K.; Quah, C. K.; Saha, P. A Colorimetric and Ratiometric Fluorescent Turn-on Fluoride Chemodosimeter and Application in Live Cell Imaging: High Selectivity via Specific SiO Cleavage in Semi Aqueous Media and Prompt Recovery of ESIPT along with the X-Ray Structures. *Tetrahedron Lett.* **2014**, *55*, 2633–2638. DOI: 10.1016/j.tetlet.2014.03.003.

[13] Yang, X. F.; Huang, Q.; Zhong, Y.; Li, Z.; Li, H.; Lowry, M.; Escobedo, J. O.; Strongin, R. M. A Dual Emission Fluorescent Probe Enables Simultaneous Detection of Glutathione and Cysteine/Homocysteine. *Chem. Sci.* **2014**, *5*, 2177–2183. DOI: 10.1039/c4sc00308j.

[14] Ren, Y.; Fan, D.; Ying, H.; Li, X. Rational Design of the Benzothiazole-Based Fluorescent Scaffold for Tunable Emission. *Tetrahedron Lett.* **2019**, *60*, 1060–1065. DOI: 10.1016/j.tetlet.2019.03.029.

[15] Patil, V. S.; Padalkar, V. S.; Tathe, A. B.; Gupta, V. D.; Sekar, N. Synthesis, Photo-physical and DFT Studies of ESIPT Inspired Novel 2-(2',4'-dihydroxyphenyl) Benzimidazole, Benzoxazole and Benzothiazole. *J. Fluoresc.* **2013**, *23*, 1019–1029. DOI: 10.1007/s10895-013-1228-4.

[16] Liu, Z.; Wang, Q.; Wang, H.; Su, W.; Dong, S. A Chloroacetate Based Ratiometric Fluorescent Probe for Cysteine Detection in Biosystems. *Tetrahedron Lett.* **2019**, *60*, 151218. DOI: 10.1016/j.tetlet.2019.151218.

[17] Li, M.; Chen, H.; Liu, X.; Wang, Y.; Zhang, N.; Zheng, K. Development of Three Novel Benzothiazole-Based Ratiometric Fluorescent Chemosensor for Detecting of Hydrazine in Serum and Gas Phase via ESIPT Process and Different Recognition Sites. *Tetrahedron Lett.* **2019**, *60*, 151219. DOI: 10.1016/j.tetlet.2019.151219.

[18] Kim, Y. H.; Roh, S. G.; Jung, S. D.; Chung, M. A.; Kim, H. K.; Cho, D. W. Excited-state Intramolecular Proton Transfer on 2-(2'-hydroxy-4'-R-phenyl)benzothiazole Nanoparticles and Fluorescence Wavelength Depending on Substituent and Temperature. *Photochem. Photobiol. Sci.* **2010**, *9*, 722–729. DOI: 10.1039/b9pp00102f.

[19] Chaudhuri, A.; Venkatesh, Y.; Jena, B. C.; Behara, K. K.; Mandal, M.; Singh, N. D. P. Real-Time Monitoring of a Photoactivated Hydrogen Persulfide Donor for Biological Entities. *Org. Biomol. Chem.* **2019**, *17*, 8800–8805. DOI: 10.1039/c9ob01982k.

[20] Banerjee, S.; Payra, S.; Saha, A. A Review on Synthesis of Benzothiazole Derivatives. *Cocat.* **2018**, *4*, 164–181. DOI: 10.2174/2213337205666180119143539.

[21] Liu, X.; Dong, Z.-B. A Review on Domino Condensation/Cyclization Reactions for the Synthesis of 2-Substituted 1,3-Benzothiazole Derivatives. *Eur. J. Org. Chem.* **2020**, *2020*, 408–419. DOI: 10.1002/ejoc.201901502.

[22] Sethiya, A.; Sahiba, N.; Soni, J.; Gandhi, D.; Agarwal, S. Contemporary Progress in the Synthesis and Reactions of 2-Arylbenzothiazole: A Review. *Coc.* **2019**, *22*, 2681–2716. DOI: 10.2174/1385272822666181122112226.

[23] Chen, G. F.; Xiao, N.; Yang, J. S.; Li, H. Y.; Chen, B. H.; Han, L. F. A Simple and Eco-Friendly Process Catalyzed by Montmorillonite K-10, with Air as Oxidant, for Synthesis of 2-Substituted Benzothiazoles. *Res. Chem. Intermed.* **2015**, *41*, 5159–5166. DOI: 10.1007/s11164-014-1619-4.

[24] Kiprof, P.; Carlson, J. C.; Anderson, D. R.; Nemykin, V. N. Systematic Color Tuning of a Family of Luminescent Azole-Based Organoboron Compounds Suitable for OLED Applications. *Dalton Trans.* **2013**, *42*, 15120–15132. DOI: 10.1039/c3dt51853a.

[25] Coelho, F. L.; Campo, L. F. Synthesis of 2-Arylbenzothiazoles via Direct Condensation between in Situ Generated 2-Aminothiophenol from Disulfide Cleavage and Carboxylic Acids. *Tetrahedron Lett.* **2017**, *58*, 2330–2333. DOI: 10.1016/j.tetlet.2017.04.078.

[26] Weekes, A. A.; Bagley, M. C.; Westwell, A. D. An Efficient Synthetic Route to Biologically Relevant 2- Phenylbenzothiazoles Substituted on the Benzothiazole Ring. *Tetrahedron.* **2011**, *67*, 7743–7747. DOI: 10.1016/j.tet.2011.08.004.

[27] Kalkhambkar, R. G.; Laali, K. K. Pd(OAc) 2 Catalyzed Synthesis of 2-Aryl- and 2-Heteroaryl- Benzoxazoles and Benzothiazoles in Imidazolium Ionic Liquids (ILs) without Additives and with Recycling/Reuse of the IL. *Tetrahedron Lett.* **2012**, *53*, 4212–4215. DOI: 10.1016/j.tetlet.2012.05.155.

[28] Bouchet, L. M.; Heredia, A. A.; Argüello, J. E.; Schmidt, L. C. Riboflavin as Photoredox Catalyst in the Cyclization of Thiobenzanilides: Synthesis of 2-Substituted Benzothiazoles. *Org. Lett.* **2020**, *22*, 610–614. DOI: 10.1021/acs.orglett.9b04384.

[29] Wang, X.; Miao, D.; Li, X.; Hu, R.; Yang, Z.; Gu, R.; Han, S. Elemental Sulfur Mediated Cyclization via Redox Strategy: Synthesis of Benzothiazoles from o-Chloronitrobenzenes and Benzyl Chlorides. *Tetrahedron.* **2017**, *73*, 5194–5199. DOI: 10.1016/j.tet.2017.07.013.

[30] Yang, Z.; Hu, R.; Li, X.; Wang, X.; Gu, R.; Han, S. One-Pot Copper-Catalyzed Synthesis of 2-Substituted Benzothiazoles from 2-Iodoanilines, Benzyl Chlorides and Elemental Sulfur. *Tetrahedron Lett.* **2017**, *58*, 2366–2369. DOI: 10.1016/j.tetlet.2017.05.004.

[31] Huang, Y.; Zhou, P.; Wu, W.; Jiang, H. Selective Construction of 2-Substituted Benzothiazoles from o-Iodoaniline Derivatives S8 and N-Tosylhydrazones. *J. Org. Chem.* **2018**, *83*, 2460–2466. DOI: 10.1021/acs.joc.7b03118.

[32] Zhang, J.; Qiao, M.; Chen, L.; Dong, Y.; Jiao, C.; Liao, S.; Wu, Y. Thiol Substrate-Promoted Dehydrogenative Cyclization of Arylmethyl Thiols with: Ortho -Substituted Amines: A Universal Approach to Heteroaromatic Compounds. *Org. Chem. Front.* **2019**, *6*, 2844–2849. DOI: 10.1039/C9QO00554D.

[33] Zhang, J.; Zhao, X.; Liu, P.; Sun, P. TBHP/KI-Promoted Annulation of Anilines, Ethers, and Elemental Sulfur: Access to 2-Aryl-, 2-Heteroaryl-, or 2-Alkyl-Substituted Benzothiazoles. *J. Org. Chem.* **2019**, *84*, 12596–12605. DOI: 10.1021/acs.joc.9b02145.

[34] Arora, A.; Weaver, J. D. Photocatalytic Generation of 2-Azolyl Radicals: Intermediates for the Azolylation of Arenes and Heteroarenes via C–H Functionalization. *Org. Lett.* **2016**, *18*, 3996–3999. DOI: 10.1021/acs.orglett.6b01718.

[35] Cheung, C. W.; Buchwald, S. L. Palladium-Catalyzed Hydroxylation of Aryl and Heteroaryl Halides Enabled by the Use of a Palladacycle Precatalyst. *J. Org. Chem.* **2014**, *79*, 5351–5358. DOI: 10.1021/jo500662s.

[36] Ranjit, S.; Liu, X. Direct Arylation of Benzothiazoles and Benzoxazoles with Aryl Boronic Acids. *Chemistry* **2011**, *17*, 1105–1108. DOI: 10.1002/chem.201002787.

[37] Yang, P.; Wang, R.; Wu, H.; Du, Z.; Fu, Y. Pd-Catalyzed C−H Arylation of Benzothiazoles with Diaryliodonium Salt: One-Pot Synthesis of 2-Arylbenzothiazoles. *Asian J. Org. Chem.* **2017**, *6*, 184–188. DOI: 10.1002/ajoc.201600514.

[38] Yang, B.; Wang, Z. X. Transition-Metal-Free Cross-Coupling of Aryl and Heteroaryl Thiols with Arylzinc Reagents. *Org. Lett.* **2017**, *19*, 6220–6223. DOI: 10.1021/acs.orglett.7b03145.

[39] Stremski, Y.; Statkova-Abeghe, S.; Angelov, P.; Ivanov, I. Synthesis of Camalexin and Related Analogues. *J. Heterocyclic Chem.* **2018**, *55*, 1589–1595. DOI: 10.1002/jhet.3192.

[40] Stremski, Y.; Kirkova, D.; Statkova-Abeghe, S.; Angelov, P.; Ivanov, I. Multicomponent Reactions for the Synthesis of Bis-Heterocyclic Pyrrole Derivatives. *Bulg. Chem. Commun* **2019**, *51*, 124–128.

[41] Kadari, S.; Yerrabelly, H.; Yerrabelly, J. R.; Gogula, T.; Goud, Y.; Thalari, G.; Doda, S. R. Stereoselective Total Synthesis of Paecilomycin E and F and Its Two Congeners Cochliomycin C and 6- epi-Cochliomycin C. *Synth. Commun.* **2018**, *48*, 1867–1875. DOI: 10.1080/00397911.2018.1472282.

[42] Mohapatra, D. K.; Reddy, D. S.; Mallampudi, N. A.; Gaddam, J.; Polepalli, S.; Jain, N.; Yadav, J. S. The Protecting-group Directed Diastereoselective Nozaki-Hiyama-Kishi (NHK) Reaction: Total Synthesis and Biological Evaluation of Zeaenol, 7-epi-zeaenol and Its Analogues. *Org. Biomol. Chem.* **2014**, *12*, 9683–9695. DOI: 10.1039/C4OB01811G.