Direct conversion of alkyl halides into benzimidazoles using pyridine-*N*-oxide and 1,2-diaminobenzenes

George Bratulescu

*Department of Organic Chemistry, University of Craiova, 13 A. I. Cuza, 200585 Craiova, Romani
Email: georgebratulescu@yahoo.com*

Abstract

Benzimidazole heterocycles were obtained from halogenated compounds and aromatic 1,2-diamines. A mild oxidizing reagent such as pyridine *N*-oxide (PyO) is required to produce the benzimidazole core. The method is solvent free and provides products without the need for chromatography. Good yields, moderate reaction temperature, fast reaction rates are important advantages of this procedure.
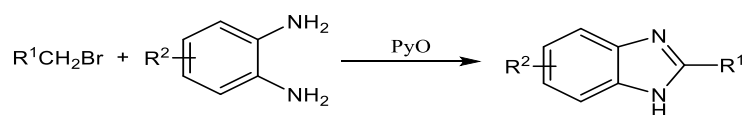
Keywords: Convergent reactions, benzimidazole, organic halides, *o*-aminoanilines, pyridine *N*-oxide, heterogeneous medium, oxidation

Introduction

Many important biological compounds contain the benzimidazole skeleton.[1] Benzimidazoles are valuable pharmacophores in compounds employed for the treatment of various human and animal diseases.[2, 3]

Benzimidazole derivatives are used as anti-inflammatory analgesic agents,[4] giardicidal drugs,[5] phosphorylase inhibitors,[6] HIV-1 RT inhibitors,[7] anti-hypertensive agents,[8] histamine H_3 receptor ligands,[9] anti-bacterial and antifungal agents,[10] anti-ulcer drugs[11] and anti-tumour agents.[12] Only benzimidazoles substituted at positions 1, 2 and 5 of the core reveal high antimicrobial activity.[13]

Many benzimidazole derivatives form complexes with transition metal cations and also have interesting pharmacological properties.[14,15] Silver(I) complexes containing V-shaped bis-benzimidazole ligands exhibit antioxidant activity and DNA-binding properties.[16] Benzimidazole-based copper and zinc complexes display analgesic, antipyretic, anti-inflammatory,[17] antitumor[18] and nuclease activity.[19, 20] Some of the d_{10} transition metal coordination polymers based on bis(benzimidazole) ligands show luminescent properties[21] and cobalt(II) benzimidazole complexes have been used as catalysts in polymerization reactions.[22]

Benzimidazoles are usually synthesized by condensation between carboxylic acids or their functional derivatives and *o*-aminoanilines.[23-28] The major drawbacks of these procedures are severe dehydrating reaction conditions, high temperature, considerable reaction time up to one day, and very strong acid catalysts.

Domino Mitsunobu reactions,[29] intramolecular cyclization of *o*-bromoaryl derivatives using copper(II) oxide nanoparticles in DMSO,[30] and the intramolecular cyclocondensation of the common arylamino oximes in the presence of methanesulfonyl chloride and triethylamine[31] can also be used to produce benzimidazole derivatives. However, all these synthetic routes require expensive metal catalysts, toxic solvents and a long reaction time up to 50 hours.

Reductive cyclization of *o*-nitroarylamines with aldehydes using sodium dithionite[32,33] or formic acid, iron powder and NH_4Cl[34] leads to benzimidazole derivatives. These procedures use a large amount of reducing agent which leads to waste at the end of the synthesis.

Oxidative methods have also been implemented for benzimidazole preparation from Schiff bases of aldehydes and *ortho*-phenylenediamines. The oxidizing agent carries out dehydrocyclization of an imine intermediate. Some of the most employed oxidants are hypervalent iodine,[35] hydrogen peroxide,[36] Oxone,[37] air,[38] lead tetraacetate,[39] potassium ferricyanide,[40] nitrogen dioxide and ozone,[41] zirconyl chloride octahydrate/ montmorillonite K-10,[42]. These procedures have important drawbacks such as laborious work-up, difficult benzimidazole purification, toxic byproducts containing heavy metals and low yields.

Recently, a patent described a method for benzimidazole preparation starting from *o*-aminoanilines, organic halides, DMSO and copper halide and sodium bicarbonate as catalysts. The protocol employs huge amounts of hazardous organic solvents and the reaction needs one day to produce the benzimidazoles.[43]

Results and Discussion

We accomplished the synthesis of benzimidazole derivatives starting from a benzylic halide and a 1,2-phenylenediamine. This is the first method of synthesis of benzimidazoles from organic halides by means of pyridine *N*-oxide (PyO) involving a one-pot reaction without catalyst or solvent (Scheme 1).
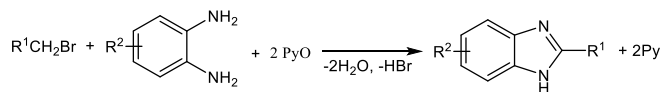
Scheme 1 One-pot three component process for benzimidazole synthesis.

To establish optimal experimental conditions for synthesis of the benzimidazole derivatives, we first studied the reaction between *o*-phenylenediamine, 1-(bromomethyl)-4-methylbenzene and pyridine *N*-oxide to obtain 2-(*p*-tolyl)-1*H*-benzimidazole. The reaction was conducted at different temperatures and stoichiometry of reactants and reagent to establish a yield of product and a reaction time, Table 1.

Optimal conditions were found to be an equimolar ration of reactants with 2.5 eq of PyO, which at 105 °C gave the best yield of 78% after 2 hours (Table 1, entry 6).

Table 1. Study of reaction conditions for 2-(*p*-tolyl)-1*H*-benzoimidazole synthesis

| Entry	Molar ratio			Time,	T,	Yield,
	o-phenylenediamine	*p*-MeC$_6$H$_4$CH$_2$Br	pyridine *N*-oxide	min.	°C	%
1	1	1	1	160	100	31
2	2	1	1	150	110	76
3	1	1	1.5	130	105	52
4	1	1.5	1	140	110	56
5	1	1	2	120	105	75
6	**1**	**1**	**2.5**	**120**	**105**	**78**
7	1	1	2.5	125	100	71
8	1	1	2.5	130	105	77
9	1.5	1	2.5	120	105	77
10	1	1.5	2.5	140	110	68
11	2	1	2.5	150	110	78

Mechanistically, it is reasonable to postulate that 4-methylbenzyl bromide is transformed into 4-methylbenzaldehyde (A) by means of PyO (Scheme 2), akin to a Kornblum reaction achieved under mild conditions.[44] The condensation reaction between 4-methylbenzaldehyde and *o*-phenylenediamine gives the Schiff base, 2-((4-methylbenzylidene)amino)aniline (B). Next, the Schiff base undergoes an intramolecular nucleophilic addition to give 2-(*p*-tolyl)-2,3-dihydro-1*H*-benzimidazole (C). The oxidation of 2-(*p*-tolyl)-2,3-dihydro-1*H*-benzimidazole by PyO leads to 2-(*p*-tolyl)-1*H*-benzimidazole (D).

Using the optimal condition for 2-(*p*-tolyl)-1*H*- benzimidazole synthesis a number of benzimidazoles were prepared. In general, the yields obtained were high (Table 2). The experimental conditions such as the molar ratio of reactants, temperature, the nature of reagents, amine and organic halide, and the reaction time influence the amount of benzimidazole product.

Electron-withdrawing groups attached to the aromatic ring of the bromide such as a nitro substituent, increase the electrophilic character of the primary carbon atom, increasing the rate of alkylation with PyO and facilitatating the formation of the aldehyde intermediate. Similarly, electron-donating groups on the aromatic ring of the diamine of the *o*-phenylenediamine such as alkyl, methoxy and halogen substituents increase amine nucleophilicity , resulting in an increase in the rate of formation of the intermediate Schiff base and the subsequent intramolecular cyclization to afford the 2,3-dihydro-1*H*-benzoimidazole derivative. Moreover, the

reducing strength of the 2,3-dihydro-1*H*-benzoimidazole derivative increases and the oxidation reaction with PyO occurs more easily in the presence of an electron-donating group. In both cases the reaction yield of the benzimidazole product increases notably (Table 2, entries 4, 5 and 10).

The method that we have developed uses a benzylic bromide and an aromatic 1,2-diamine in stoichiometric ratio. The method provides an alternative route for benzimidazole preparation in a dry medium by a convergent reaction. The benzimidazole products were easily purified by recrystallization from solvents such as ethanol–water mixtures. Moreover toxic hydrogen bromide is not released during the reaction but is trapped by the pyridine generated during the process.
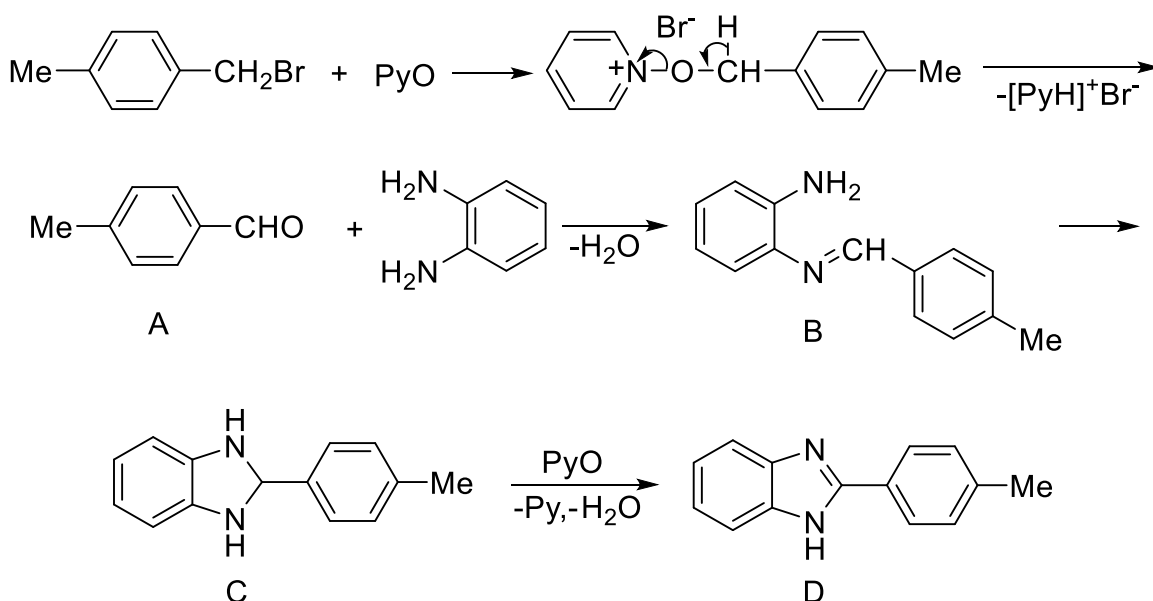
Scheme 2. Plausible mechanism for 2-(*p*-tolyl)-1*H*-benzimidazole synthesis.

Table 2. Benzimidazole derivatives (**3**) obtained under mild conditions
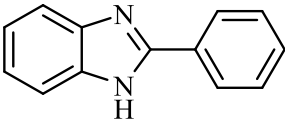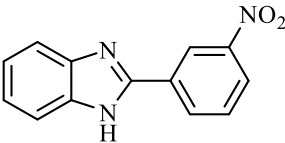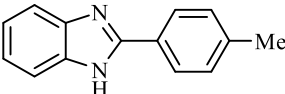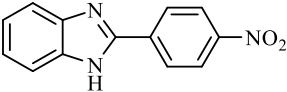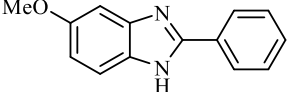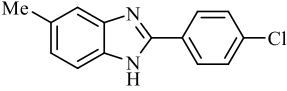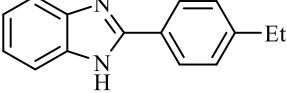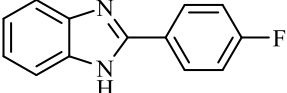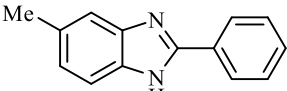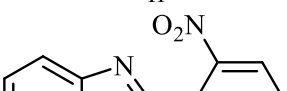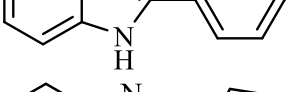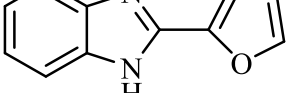
Product **3**	Time, min	T, °C	Yield,[a] %
3a	120	105	80
3b	120	80	81
3c	120	105	78

Table 2. Continued

Product **3**		Time, min	T, °C	Yield,a %
3d	benzimidazole-2-yl-phenyl-NO₂ structure	120	110	90
3e	MeO-benzimidazole-2-yl-phenyl structure	120	105	85
3f	Me-benzimidazole-2-yl-phenyl-Cl structure	120	105	78
3g	benzimidazole-2-yl-phenyl-Et structure	120	105	77
3h	benzimidazole-2-yl-phenyl-F structure	190	105	77
3i	Me-benzimidazole-2-yl-phenyl structure	120	110	83
3j	benzimidazole-2-yl-phenyl-O₂N structure	120	95	92
3k	benzimidazole-2-yl-furan structure	165	100	76
3l	benzimidazole-2-yl-pyrrole structure	165	110	75

ª Isolated and unoptimized yields.

Conclusions

A new procedure for conversion of benzyl bromides into benzimidazole derivatives was developed. Benzimidazoles were synthesized by a one-pot three-component reaction starting from benzyl bromides, *o*-phenylenediamines and pyridine *N*-oxide. The synthesis does not require catalysts and solvents. The procedure constitutes an alternative to current methods that all use either hazardous catalysts or toxic organic solvents as reaction media and separation of benzimidazoles by chromatographic techniques. Important benefits of the method are also a significantly short reaction time, moderate temperature, and lower energy consumption than in the other methods.

Experimental Section

General. Organic bromides, *ortho*-phenylenediamine, pyridine *N*-oxide are commercial compounds. The synthesized products were identified by TLC (EtOAc-petroleum ether) and ¹H-NMR. The ¹H-NMR spectra were

recorded on a BRUKER ARX instrument (300 MHz). DMSO-d_6 was used as the solvent and tetramethylsilane as an internal standard. The melting points were determined on a Gallenkamp digital melting point apparatus.

General procedure for benzimidazole (3) synthesis

Primary alkyl bromide derivative (5 mmol [**1a**: 0.855 g; **1b**: 1.08 g; **1c**: 0.925 g; **1d**: 1.08 g; **1a**: 0.855 g; **1e**: 1.027 g; **1f**: 0.995 g; **1g**: 0.945 g; **1a**: 0.855 h; **1j**: 1.08 g; **1i**: 0.805; **1j**: 0.8 g]), pyridine *N*-oxide (12.5 mmol; 1.187 g) and *ortho*-phenylenediamine derivative (5 mmol [**2a**: 0.54 g; **2a**: 0.54 g; **2a**: 0.54 g; **2a**: 0.54 g; **2b**: 0.69 g; **2c**: 0.61 g; **2a**: 0.54 g; **2a**: 0.54 g; **2c**: 0.61 g; **2a**: 0.54 g; **2a**: 0.54; **2a**: 0.54 g]) were well mixed in a 25 mL round bottomed flask and placed in an oil bath on a magnetic stirrer hot plate at the required temperature. The mixture was heated to the selected temperature for the required time (Table 2). After completion of the reaction (TLC, EtOAc-petroleum ether 7:3), the organic mixture was washed with dilute aq NaOH, and the precipitated product filtered off. The resulting residue was recrystallized from EtOH-H_2O to give the desired benzimidazole products (**3**).

    All of the products are known compounds and their identity was easily confirmed by comparison with authentic samples.

2-Phenyl-1H-benzimidazole (3a). Mp 292-293 °C(Lit.[45] 292 °C). ^{1}H-NMR: δ 7.24 (d, *J* 6.0, 2H), 7.42-7.61 (m, 5H), 8.15 (d, *J* 6.0, 2H), 12.97 (br, s, 1H). The ^{1}H-NMR data of the literature[46] δ 7.22–7.25 (2H, m, ArH), 7.48–7.60 (5H, m, ArH), 8.21–8.24 (2H, m, ArH).

2-(3-Nitrophenyl)-1H-benzimidazole (3b). Mp 204-205 °C (Lit.[47] 203-205 °C). ^{1}H-NMR: δ 7.19 (m, 2H), 7.50 (m, 2H), 7.71 (t, *J* 7.2, *J* 6.9, 1H), 8.10 (d, *J* 7.2, 1H), 8.50 (d, *J* 6.9, 1H), 8.89 (s, 1H), 12.87 (br, s, 1H, NH). The ^{1}H-NMR data of the literature[48] δ 12.9 (s, 1H, NH), 8.90 (s, 1H), 8.50 (d, 1H, *J* 6.9 Hz), 8.10 (d, 1H, *J* 7.2 Hz), 7.70 (t, 1H, *J* 7.2, 6.9 Hz), 7.50 (m, 2H), 7.2 (m, 2H).

2-p-Tolyl-1H-benzimidazole (3c). Mp 269-270 °C (Lit.[45] 270 °C). ^{1}H-NMR: δ 2.38 (s, 3H), 7.21 (dd, *J* 6.1, *J* 3.2, 2H, 2H), 7.36 (d, *J* 8.0, 2H), 7.52-7.66 (m, 2H), 8.07 (d, *J* 7.6, 2H), 12.82 (s, 1H). The ^{1}H-NMR data of the literature[49] δ 12.83 (br, s, 1H, NH), 8.09–8.07 (d, 2H, *J* 7.6 Hz), 7.65–7.53 (m, 2H), 7.37–7.35 (d, 2H, *J* 8.0 Hz), 7.20 (m, 2H), 2.39 (s, 3H).

2-(4-Nitrophenyl)-1H-benzimidazole (3d). Mp 314-314.5 °C (Lit.[50] 312–314 °C). ^{1}H-NMR: δ 7.13 (m, 1H), 7.26 (m, 1H), 8.04 (m, 3H), 8.30 (d, *J* 6.4 Hz, 2 H), 8.55 (s, 1H), 13.4 (br, s, 1H, NH). The ^{1}H-NMR data of the literature[50] δ 7.20-7.60 (6H, m, ArH), 8.00-8.08 (2H, m, ArH).

5-Methoxy-2-phenyl-1H-benzoimidazole (3e). Mp 150-151 °C (Lit.[49] 148-150 °C). ^{1}H-NMR: δ 3.82 (s, 3H), 7.01 (m, 1H), 7.08–7.23 (m, 1H), 7.47-7.59 (m, 4H), 8.11-8.30 (m, 2H), 13.05 (s, 1H, NH). The ^{1}H-NMR data of the literature[49] δ 13.07 (br s, 1H), 8.29–8.13 (m, 2H), 7.58–7.48 (m, 4H), 7.25–7.08 (m, 1H), 7.02–7.01 (m, 1H), 3.83–3.82 (s, 3H).

2-(4-Chlorophenyl)-5-methyl-1H-benzimidazole (3f). Mp 223-224 °C (Lit.[51] 224-225 °C). ^{1}H-NMR: δ 2.42 (s, 3H, CH_3), 7.22 (d, *J* 3, 1H), 7.62-7.67 (m, 4H), 8.03 (d, *J* 8.4, 2H), 12.8 (br, s, 1H, NH). The ^{1}H-NMR data of the literature[51] δ= 12.79 (s, 1H), 8.03 (d, *J* 8.45 Hz, 2H), 7.64-7.66 (m, 4H), 7.23 (d, *J* 3.05 Hz, 1H), 2.42 (s, 3H).

2-(4-Ethylphenyl)-1H-benzimidazole (3g). Mp 145-146 °C (Lit.[51] 143-145 °C). ^{1}H-NMR: δ 1.24 (t, *J* 7.8, 3H, CH_3), 2.67 (q, *J* 7.8, 2H, CH_2), 7.14-7.17 (m, 2H), 7.35 (d, *J* 8.0, 2H), 7.53 (d, *J* 8.4, 1H), 7.66 (d, *J* 8.8, 1H), 8.06 (d, *J* 8.4, 2H), 12.8 (br, s, 1H, NH). The ^{1}H-NMR data of the literature[51] δ 12.82 (s, 1H), 8.06 (d, *J* 8.40 Hz, 2H), 7.67 (d, *J* 8.80 Hz, 1H), 7.53 (d, *J* 8.40 Hz, 1H), 7.35 (d, *J* 8.00 Hz, 2H), 7.15-7.17 (m, 2H), 2.67 (d, *J* 7.60 Hz, 2H), 1.25 (t, *J* 7.80 Hz, 3H).

2-(4-Fluorophenyl)-1H-benzimidazole (3h). Mp 250.5-251 °C (Lit.[52] 250-251 °C). ^{1}H-NMR: δ 7.15-7.18 (m, 2H), 7.21-7.25 (m, 4H), 8.01 (m, 2H), 12.95 (s, 1H). The ^{1}H-NMR data of the literature[51] δ 12.95 (s, 1H), 8.00-8.02 (m, 2H), 7.23-7.25 (m, 4H), 7.15-7.17 (m, 2H).

5-Methyl-2-phenyl-1H-benzimidazole (3i). Mp 243-245 °C (Lit.[53] 243-245 °C). ^{1}H-NMR: δ 2.42 (s, 3H), 7.06 (d, *J* 7.0, 1H), 7.43–7.53 (m, 5H), 8.13 (d, *J* 7.0, 2H), 12.81 (br, s, 1H). The ^{1}H-NMR data of the literature[53] δ 12.72 (br s, 1H), 8.13 (d, *J* 6.9 Hz, 2H), 7.45–7.55 (m, 5H), 7.00 (d, *J* 7.0 Hz, 1H), 2.41 (s, 3H).

2-(2-Nitrophenyl)-1H-benzimidazole (3j). Mp 209-210 °C (Lit.[45] 210 °C). ^{1}H-NMR: δ 7.21 (m, 1H), 7.26-7.61 (m, 5H), 8.00-8.09 (m, 2H), 11.86 (br,s, 1H, NH). The ^{1}H-NMR data of the literature[50] δ 7.20–7.60 (6H, m, Ar), 8.00–8.08 (2H,m, Ar).

2-(Furan-2-yl)-1H-benzimidazole (3k). Mp 286-287 °C (Lit.[49] 285–286 °C). ^{1}H-NMR: δ=6.72 (dd, *J* 3.3, *J* 1.8, 1H), 7.20–7.25 (m, 3H), 7.53 (s, 2H), 7.95 (dd, J =1.8, *J* 0.9, 1H), 12.87 (br, s, 1H, NH). The ^{1}H-NMR data of the literature[49] δ 12.92 (br s, 1H), 7.95 (dd, *J* 1.8, 0.9 Hz, 1H), 7.55 (br s, 2H), 7.24–7.20 (m, 3H), 6.73 (dd, J =3.3, 1.8 Hz, 1H).

2-(1H-pyrrol-2-yl)-1H-benzimidazole (3l). Mp 262-262.5 °C (Lit.[54] mp 261–262 °C). ^{1}H-NMR: δ 6.56 (dd, *J* 8.8, *J* 3.8, 1H), 6.80 (d, *J* 8.8, 1H), 7.19 (m, 2H, Ar), 7.34 (d, *J* 3.8 Hz, 1H), 7.50 (m, 2H, ArH), 9.8 (br s, 2H, NH). The ^{1}H-NMR data of the literature[54] δ= 9.76 (br s, 2 H, NH), 7.48 (m, 2 H, Ar), 7.33 (d, *J* 3.8 Hz, 1 H,), 7.22 (m, 2H, Ar), 6.80 (d, *J* 8.8 Hz, 1H,), 6.58 (dd, *J* 3.8 Hz, *J* 8.8 Hz, 1 H).

References

1.   Gaba, M.; Mohan, C. *Med. Chem. Res*. **2016**, *25*, 173-210.
     https://doi.org/10.1007/s00044-015-1495-5

2.   Keri, R. S.; Hiremathad, A.; Budagumpi, S.; Nagaraja, B. M. *Chem. Biol. Drug*. **2015**, *86*, 799-845.

3.   Yadav, G.; Ganguly, S. *Eur. J. Med. Chem*. **2015**, *97*, 419-43.
     https://doi.org/10.1016/j.ejmech.2014.11.053

4.   Gaba, M.; Gaba, P.; Uppal, D.; Dhingra, N.; Bahia, M. S.; Silakari, O.; Mohan, C. *Acta Pharm. Sin. B* **2015**, *4*, 337-342.
     https://doi.org/10.1016/j.apsb.2015.05.003

5.   Hernandez-Covarrubias, C.; Vilchis-Reyes, M. A.; Yepez-Mulia, L.; Sanchez-Diaz, R.; Navarrete-Vazquez, G.; Hernandez-Campos, A.; Castillo, R.; Hernandez-Luis, F. *Eur. J. Med. Chem.* **2012**, *52*, 193-204.
     https://doi.org/10.1016/j.ejmech.2012.03.014

6.   Alvarez, F.; Gherardi, A.; Nebois, P.; Sarciron, M. E.; Petavy, A. F.; Walchshofer, N. Bioorg. *Med. Chem. Lett*. **2002**, *12*, 977-979.
     https://doi.org/10.1016/S0960-894X(02)00064-1

7.   Rao, A.; Chimirri, A.; Ferro, S.; Monforte, A. M.; Monforte, P.; Zappala, M. *Arkivoc* **2004**, (v), 147-155.

8.   Yang, H.; Zhang, T.; Zhang, X. (Kelun Pharm Res Co Ltd). *CN 102295604-A*, December 28, 2011.

9.   Aslanian, R.; Zhu, X.; Vaccaro, H. A.; Shih, N. Y.; Piwinski, J. J.; Williams, S. M.; West, R. E. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 5032-5036.
     https://doi.org/10.1016/j.bmcl.2008.08.008

10. Soni, L. K.; Narsinghani, T.; Sethi, A. *Med. Chem. Res*. **2012**, *21*, 4330-4334.
     https://doi.org/10.1007/s00044-012-9976-2

11. Spitz M. (Mepha AG). *CH 699254-B1*, February 15, 2010.

12. Kamal, A.; Praveen Kumar, P.; Seshadri, B. N.; Sreekanth, K. *US 08835421*, September 16, 2014**.**

13. Ansari, K. F.; Lal, C. *Eur. J. Med. Chem*. **2009**, *44*, 4028-4033.
     https://doi.org/10.1016/j.ejmech.2009.04.037

14. Ashraf, A.; Siddiqui, W. A.; Akbar, J.; Mustafa, G.; Krautscheid, H.; Ullah, N.; Mirza, B.; Sher, F.; Hanif, M.; Hartinger, C. G. *Inorg. Chim. Acta*. **2016**, *443*, 179-185.
https://doi.org/10.1016/j.ica.2015.12.031

15. Hu, J. Y.; Liao, C. L.; Hu, L. L.; Zhang, C. C.; Chen, S. F.; Zhao, J. A. *Russ. J. Coord. Chem.* **2015**, *41*, 212-219.
https://doi.org/10.1134/S1070328415030057

16. Wu, H. L.; Yuan, J. K.; Bai, Y.; Pan, G. L.; Wang, H.; Kong, J.; Fan, X. Y.; Liu, H. M. *Dalton Trans*. **2012**, *41*, 8829-8838.
https://doi.org/10.1039/c2dt30512g

17. AlAjmi, M.F.; Hussain, A.; Alsalme, A.; Khan, R. A. *RSC Adv*. **2016**, *6*, 19475-19481.
https://doi.org/10.1039/C5RA25071D

18. Zhao, J. A.; Li, S. S.; Zhao, D. D.; Chen, S. F.; Hu, J. Y. *J. Coord. Chem*. **2013**, 66, 1650-1660.
https://doi.org/10.1080/00958972.2013.789505

19. Gonzalez-Alvarez, M.; Alzuet, G.; Borras, J.; Macias, B.; del Olmo, M.; Liu-Gonzalez, M.; Sanz, F. *J. Inorg. Biochem*. **2002**, *89*, 29-35.
https://doi.org/10.1016/S0162-0134(01)00369-5

20. Xiangxiang, R.; Jiayang, C.; Xueyi, L. *Chin. J. Chem*. **2011**, *29*, 1380-1388.
https://doi.org/10.1002/cjoc.201180257

21. Yang, F. F.; Yu, X. Y.; Luo, Y. H.; Wang, X. F.; Sun, D. H.; Zhang, H. *Polyhedron* **2015**, *85*, 337-346.
https://doi.org/10.1016/j.poly.2014.08.002

22. Tartea, N. H.; Woo, S. I.; Cuia, L.; Gong, Y. D.; Hwang, Y. H. *J. Organomet. Chem*. **2008**, *693*, 729–736.
https://doi.org/10.1016/j.jorganchem.2007.12.001

23. Wagner, E. C.; Millett, W. H. Benzimidazole. *Org. Synth., Coll. Vol*. **1943**, *2*, 65.

24. Grimmet, M. R.; Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, **1984**, Vol. *5*, pp 104-105.

25. Panda, S. S., Malik, R.; Jain, S. C. *Curr.Org. Chem*. **2012**, *16*, 1905-1919.
https://doi.org/10.2174/138527212802651232

26. Cee, V. J.; Downing, N. S. *Tetrahedron Lett*. **2006**, *47*, 3747-3750.
https://doi.org/10.1016/j.tetlet.2006.03.112

27. Sluiter, J.; Christoffers, J. *Synlett* **2009**, *1*, 63-66.

28. Bastug, G.; Eviolitte, C.; Markó; I. E. *Org. Lett*. **2012**, *14*, 3502-3505.
https://doi.org/10.1021/ol301472a

29. Yan, Y.; Zhong, Q. F.; Zhao, N.; Liu, G. *Mol. Divers*. **2012**, *16*, 157-162.
https://doi.org/10.1007/s11030-011-9343-0

30. Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719-8725.
https://doi.org/10.1021/jo901813g

31. Wray, B. C.; Stambuli, J. P. *Org. Lett*. **2010**, *12*, 4576-4579.
https://doi.org/10.1021/ol101899q

32. Oda, S; Shimizu, H.; Aoyama, Y.; Ueki, T. ; Shimizu, S.; Osato, H.; Takeuchi, Y. *Org. Process Res. Dev*. **2012**, *16*, 96-101.
https://doi.org/10.1021/op200251c

33. Yang, D.; Fokas, J.; Li, J.; Yu, L.; Baldino, C. M. *Synthesis* **2005**, *1*, 47-56.
https://doi.org/10.1055/s-2004-834926

34. Hanan, E. J.; Chan, B. K.; Estrada, A. A.; Shore, D. G.; Lyssikatos, J. P. *Synlett* **2010**, *18*, 2759-2764.

https://doi.org/10.1055/s-0030-1259007

35. Rao, D. N.; Rasheed, S.; Vishwakarma, R. A.; Das, P. *RSC Adv*. **2014**, *4*, 25600-25604.
https://doi.org/10.1039/c4ra02279c

36. Bahrami, K.; Khodaei, M. M.; Kavianinia I. *Synthesis* **2007**, 417-427.

37. Beaulieu, P. L.; Haché, B.; von Moos, E. *Synthesis* **2003**, 1683-1692.
https://doi.org/10.1055/s-2003-40888

38. Nguyen, K. M. H.; Largeron, M. *Eur. J. Org. Chem*. **2016**, *5*, 1025-1032.
https://doi.org/10.1002/ejoc.201501520

39. Stephens, F. F.; Bower, J. D. *J. Chem. Soc*. **1949**, *27*, 2971-2972.
https://doi.org/10.1039/jr9490002971

40. Hutchinson, I.; Stevens, M. F. G.; Westwell, A. D. Antitumor benzothiazoles. *Tetrahedron Lett.* **2000**, *41*, 425-428.
https://doi.org/10.1016/S0040-4039(99)02076-6

41. Kaiya, T.; Nakamura, K.; Tanaka, M.; Miyata, N.; Kohda, K. *Chem. Pharm. Bull.* **2004**, *52*, 570-576.
https://doi.org/10.1248/cpb.52.570

42. Rostamizadeh, S.; Amani, A. M.; Aryan, R.; Ghaieni, H. R.; Norouzi, L. *Monatsh. Chem.* **2009**, *140*, 547-552.
https://doi.org/10.1007/s00706-008-0087-1

43. Zeng, Q.; Qiu, D. (Chengdu University of Technology). Method of synthesis of 2-arylbenzimidazoles. *CN 103755642 B,* September 30, 2015.

44. Barbry, D.; Champagne, P. *Tetrahedron Lett*. **1996**, *37*, 7725-7726.
https://doi.org/10.1016/0040-4039(96)01734-0

45. Alloum, A. B.; Bougrin, K.; Soufiaoui, M. *Tetrahedron Lett.* **2003***, 44*, 5935-5937.
https://doi.org/10.1016/S0040-4039(03)01387-X

46. Dudd, L. M.; Venardou, E.; Garcia-Verdugo, E.; Licence, P.; Blake, A. J.; Wilsona, C.; Poliakoff, M. *Green Chem*. **2003**, *5*, 187-192.
https://doi.org/10.1039/b212394k

47. Ponnala, S.; Sahu, D. P. *Synth. Commun*. **2006**, *36*, 2189-2194.
https://doi.org/10.1080/00397910600638879

48. Nagawade, R. R.; Shinde, D. B. *Chin. Chem. Lett*. **2006**, *17*, 453-456.

49. Chen, Ch.; Chen, C.; Li, B.; Tao, J.; Peng, J. *Molecules* **2012**, *17*, 12506-12520.
https://doi.org/10.3390/molecules171112506

50. Shen, M. G.; Cai, C. *J. Fluorine Chem*. **2007**, *128*, 232–235.
https://doi.org/10.1016/j.jfluchem.2007.01.009

51. Tian, M.; Wang, X. *Chinese J. Org. Chem*. **2009**, 29, 1654-1658.

52. Du, L. H.; Wang, Y. G. *Synthesis*, **2007**, *5*, 675-678.

53. Chari, M. A.; Shobha, D.; Kenawy, E. R.; Al-Deyab, S. S.; Subba Reddy, B. V.; Vinu, A. *Tetrahedron Lett*. **2010**, *51*, 5195–5199.
https://doi.org/10.1016/j.tetlet.2010.07.132

54. Trofimov, B. A.; Ivanov, A. V.; Skitaltseva, E. V.; Vasiltsov, A. M.; Ushakov, I. A.; Petrushenko , K. B.; Mikhaleva, A. I. *Synthesis* **2009**, *21*, 3603-3610.
https://doi.org/10.1055/s-0029-1216996