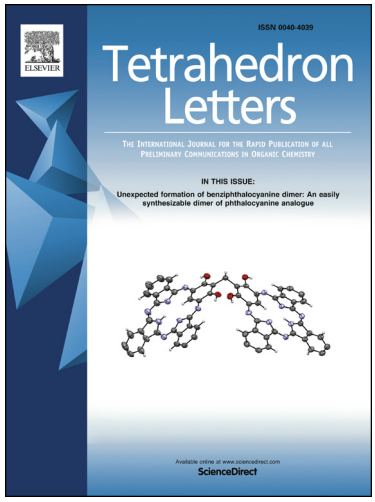


A Practical Method, NaOCl-Mediated, to Prepare Thiabendazoles via Intramolecular Amination Reaction

Vikrant Patil, Enrique Barragan, Shivaputra A. Patil, Siddappa A. Patil, Alejandro Bugarin

PII: S0040-4039(17)30944-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.07.086
Reference: TETL 49168

To appear in: *Tetrahedron Letters*

Received Date: 12 June 2017
Revised Date: 15 July 2017
Accepted Date: 24 July 2017

Please cite this article as: Patil, V., Barragan, E., Patil, S.A., Patil, S.A., Bugarin, A., A Practical Method, NaOCl-Mediated, to Prepare Thiabendazoles via Intramolecular Amination Reaction, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.07.086

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

A Practical Method, NaOCl-Mediated, to Prepare Thiabendazoles via Intramolecular Amination Reaction

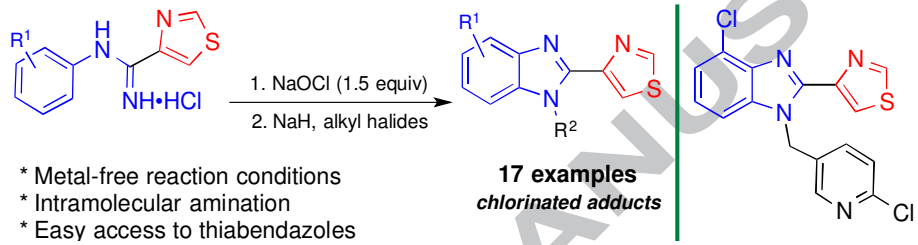
Leave this area blank for abstract info.

Vikrant Patil[a], Enrique Barragan[b], Shivaputra A. Patil[c], Siddapa A. Patil[a]*, and Alejandro Bugarin[b]*

[a]*Centre for Nano & Material Sciences, Jain University, Jain Global Campus, Bangalore 562112, Karnataka, INDIA*

[b]*Department of Chemistry and Biochemistry, University of Texas at Arlington, Arlington, TX 76019, USA*

[c]*Pharmaceutical Sciences Department, College of Pharmacy, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Road, North Chicago, IL 60064, USA*



* Metal-free reaction conditions
* Intramolecular amination
* Easy access to thiabendazoles

17 examples
chlorinated adducts

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

A Practical Method, NaOCl-Mediated, to Prepare Thiabendazoles via Intramolecular Amination Reaction

Vikrant Patil[a], Enrique Barragan[b], Shivaputra A. Patil[c], Siddappa A. Patil[a]*, Alejandro Bugarin[b]*

[a]*Centre for Nano & Material Sciences, Jain University, Jain Global Campus, Bangalore 562112, Karnataka, INDIA.*
[b]*Department of Chemistry & Biochemistry, University of Texas at Arlington, Arlington, TX 76019, USA.*
[c]*Pharmaceutical Sciences Department, College of Pharmacy, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Road, North Chicago, IL 60064, USA.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Thiabendazole
Bleach
Synthesis
Characterization
Single-crystal X-ray diffraction

ABSTRACT

A series of new chlorinated thiabendazoles (**6a-m**) have been synthesized from readily available anilines and 4-cyanothiazole in moderate to good yields. All synthesized compounds were fully characterized using ^{1}H NMR, ^{13}C NMR, IR, and mass spectrometry. Additionally, the structure of the compound (**6f**) was confirmed by single-crystal X-ray diffraction. In addition, synthesis of 2-substituted benzimidazoles and 2-phenyl benzothiazole was investigated using our optimized conditions and the outcome is presented herein.

Heterocyclic compounds are a class of cyclic molecules that have at least two different elements in their ring system.[1] Therefore, heterocycles represent what is possible the largest and more diverse class of organic compounds.[2] Heterocycles have found many miscellaneous applications including; ligands for transition state metals,[3] organocatalysts,[4] building blocks for bioactive molecules and pharmaceuticals,[5] solvents (e.g., THF, pyridine, and dioxanes), etc.[6]

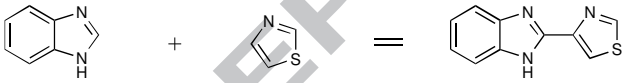


Figure 1. Structures of benzimidazole, thiazole, and thiabendazole

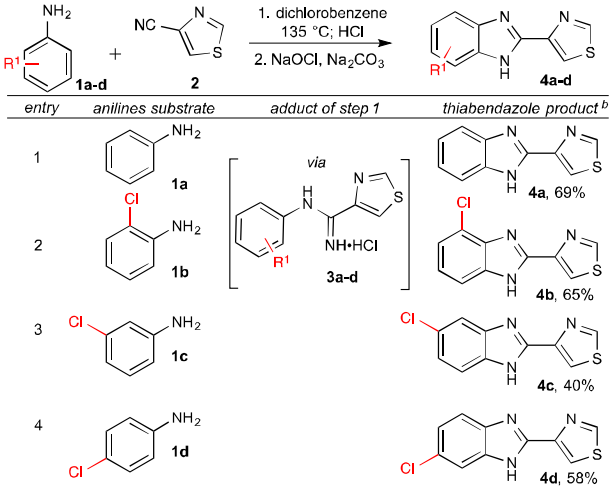
Among the vast classes of heterocyclic compounds, organic molecules containing benzimidazole and thiazole backbones in their structure (Figure 1) are of high importance in medicinal chemistry, due to their large pharmacological spectrum in both humans and animals.[7] They are valuable intermediates in the synthesis of many bioactive molecules, including thiabendazoles (Figure 1). Benzimidazole and thiazole derivatives have displayed a wide range of biological activities such as; antiangiogenesis,[8] anticancer,[9] antifungal and antibacterial.[10] Also, it has been reported that keratitis due to the fungus *Aspergillus flavus* can be treated using thiabendazole.[11] Across the globe, several research groups have reported assorted benzimidazole and thiazole derivatives as promising antimicrobial agents.[10, 12] On the other hand, only a few groups have synthesized thiabendazoles and study their biological activities. For example, Meng and co-workers, in 2015, reported the biological evaluation and synthesis of thiabendazoles via condensation of 1,2-diaminobenezene with a thiazole-4-carboxaldehyde derivative.[8] Another direct route towards thiabendazoles appeared in a U.S. patent back in 1961, which uses bleach (sodium hypochlorite).[13] However, the patent lacks reaction yields and a reliable protocol. Months later, the same group documented a small study on the antiparasitic properties of these compounds[14] and in 1970, they reported a broader biological spectrum.[15] Furthermore, Sletzinger and co-authors reported the synthesis of two thiabendazole derivatives utilizing similar protocol, albeit using a stepwise procedure, in 1965.[16] In view of these statements, it was thought worthwhile to further develop the bleach mediated synthesis of thiabendazoles, in order to investigate it scope and limitations, while analyzing the effects of chlorine atoms selectively placed on the final thiabendazole adducts.

Herein, a simple method is described for the synthesis of chlorinated thiabendazoles (Tables 1 and 2). In brief, our synthetic strategy was based on reacting substituted anilines (**1a-d**) with 4-cyanothiazole (**2**) in the presence of dry HCl gas to form the corresponding amidine derivative (**3a-d**), which were in turn cyclized to 2-(thiazol-4-yl)-1*H*-benzoimidazole derivatives (**4a-d**) via intramolecular amination reaction using stoichiometric amounts of bleach (Table 1).[17] In order to make our study more meaningful, aniline **1a** plus three more anilines bearing a chlorine atom at *ortho*, *meta*, and *para* positions **1b-c**

* Corresponding author. Tel.: +1-817-272-9399; fax: +1-817-272-3808; e-mail address: bugarin@uta.edu (A. Bugarin)

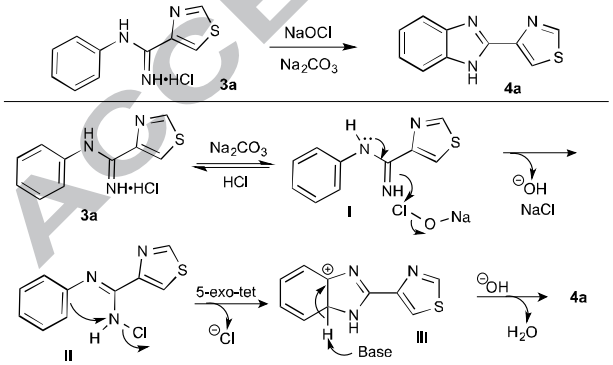
were selected. All anilines afforded their expected product in moderate to good yields, with aniline **1c** producing a lower yield due to the presence of product **4b** in the reaction mixture. Aniline **1c** afforded 40% yield of product **4c** and 17% yield of adduct **4b**. Nonetheless, both adducts were easily separated by column chromatography (Table 1).

Table 1.
Synthesis of thiabendazoles (**4a-d**)[a]



[a]Reaction conditions for step 1. Solvent = 1,2-dichlorobenzene, temp = 135 °C, aniline (**1a-d**) (49 mmol), 4-cyanothiazole (45 mmol), then dry HCl. Step 2. Solvent: methanol/water 1:1, amidine hydrochloride (**3a-d**) (31 mmol), sodium carbonate (31 mmol), NaOCl (31 mmol).
[b]Yield of purified products (average of 2-3 runs).

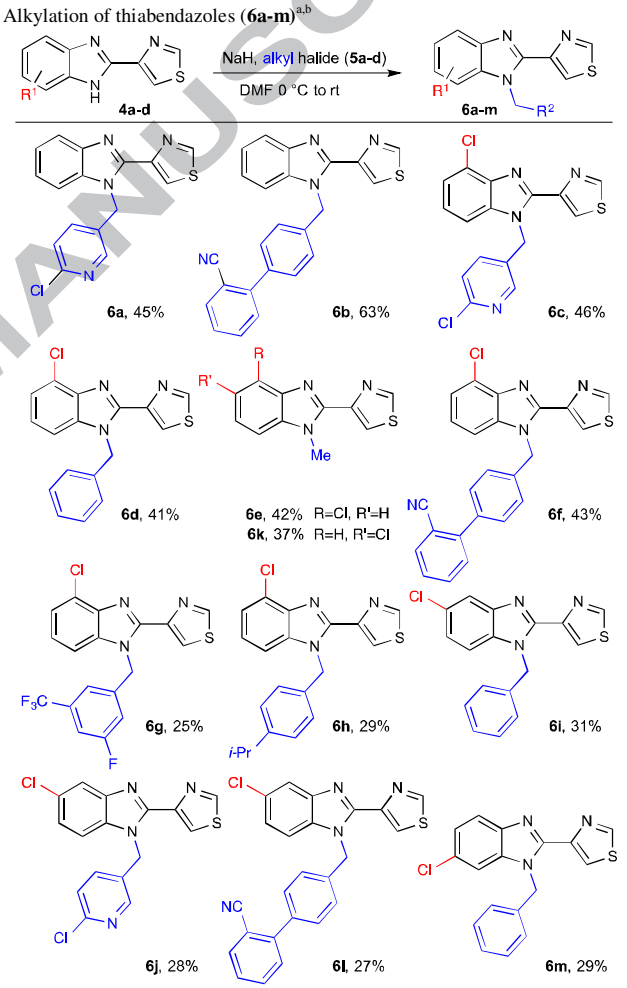
The observed thiabendazole adducts and reactivity suggests that the mechanism follows an oxidative cyclization process, as depicted on Scheme 1. First, sodium carbonate helps to dissociate the ammonium salt and release amidine **I**, which in turn reacts with sodium hypochlorite to form *N*-chloro carboximidamide **II**. Then, this intermediate undergoes a *5-exo-tet* cyclization to afford intermediate **III** that quickly re-aromatizes in the presence of base, to produce thiabendazole **4a**.[18] This represents a metal-free intramolecular amination reaction. Although, our mechanistic interpretation proposes two-electron sequences, a radical pathway it is also plausible. However, further studies, to be published later, will help to support or refuse this hypothesis.



Scheme 1. Proposed mechanism

With the four different thiabendazoles (**4a-d**) on hand, we proceeded to investigate the scope of these thiabendazoles under alkylation conditions. The outcome is reported in Table 2. For thiabendazole **4a**, two alkyl halides were employed, a pyridine and bisphenyl derivatives, both affording their respective adducts, **6a** and **6b**, in moderate to good yields (45% and 63%, respectively). The *ortho* substituted thiabendazole **4b** was reacted with six different alkyl halides to afford products **6c** to **6h** in moderate yields. In addition, the *meta* chlorinated thiabendazole **4c** was reacted with four different alkyl halides to produce adducts **6i** to **6l** in moderate yields. Finally, the *para* chlorinated thiabendazole **4d** was reacted with benzyl chloride to produce adducts **6m** in 29% yields. The low yields for these substitution reactions are attributed to two main factors, the utilization of alkyl chlorides and to over-alkylation, which formed undesired byproducts. These side products were difficult to characterize; however, we believe they are mixtures of ammonium salts.[19] Although the yields are moderate, the observed functional group tolerance is good. For example, conditions tolerated halides, heterocycles, benzylic protons, and cyano groups. Therefore, this work should generate interest in the chemistry community for the synthesis of more complex or further functionalized thiabendazoles.

Table 2.
Alkylation of thiabendazoles (**6a-m**)[a,b]



[a]Reaction conditions: solvent = DMF, temp = 25 °C, ratios: 2-(thiazol-4-yl)-1*H*-benzoimidazole (2.5 mmol)/ alkyl halide (2.7 mmol) / sodium hydride (3.0 mmol).
[b]Yield of purified products (average of 2-3 runs).

The structures of all synthesized thiabendazoles (**6a-m**) were confirmed by ^{1}H NMR, ^{13}C NMR, IR and mass spectrometry techniques. All ^{1}H NMR spectra of the chlorinated thiabendazoles (**6a-m**) present a singlet peak in the range 6.03-6.22 ppm assigned to the methylene (CH_2) protons of benzyl moiety attached to the benzimidazole nitrogen atom. This indicated a successful alkylation reaction. Likewise, ^{13}C NMR

spectra of all thiabendazoles (**6a-m**) revealed the presence of peaks in the range δ = 45.74-49.15 ppm attributed to the methylene (CH_2) carbon atom. Conversely, the IR spectra of all chlorinated thiabendazoles (**6a-m**) displayed a strong absorption band around 1304–1573 cm^{-1}, correspond to the $\nu_{(C=N)}$ stretching vibrations and a sharp band of medium intensity at 2923–3126 cm^{-1}, attributed to the aromatic $\nu_{(C-H)}$ stretching vibrations. Furthermore, the results obtained from the mass spectrometry are in good agreement with the proposed structures of the chlorinated thiabendazoles (**6a-m**).

In addition, single crystals of compound (**6f**) suitable for X-ray diffraction analysis were obtained by slow evaporation in chloroform. A perspective view of compound (**6f**) is depicted in Figure 2. Compound (**6f**) crystallized in the monoclinic space group P 2_1/n with four motifs in a unit cell. Crystal structure of compound (**6f**) revealed that the molecule is co-planar in nature. The crystals of compound (**6f**) do not have any organic solvent molecules or lattice held water molecules in the unit cell of the determined structure. The C-C bond distances in phenyl ring are in the normal range of 1.35 – 1.48 Å, which is characteristic of delocalized aromatic rings. The C-C-C bond angles in phenyl ring are close to 120°, it suggests that carbon atoms are sp^2 hybridized. The compound (**6f**) lies in three planes with plane I [C(1) C(2) C(3) C(4) C(20) C(21) C(5) Cl(1) N(1) C(14) N(2) C(22) N(4) C(23) Cl(24) and S(1)] making a dihedral angle of 75.59° and 60.92°with plane II [C(6) C(7) C(8) C(9) C(16) and C(15)], and plane III [N(3) C(19) C(18) C(10) C(17) C(13) C(12), and C(11)], whereas the plane II forms a dihedral angle of 47.00° with plane III. The molecular packing diagram shows four layers of molecules, which are independently arranged in the unit cell. In each layer, the molecules are alternatively parallel. The molecular packing diagram did not show involvement of intramolecular or intermolecular hydrogen bonding. Hence, molecules forming each layer are not connected through intermolecular hydrogen bonding.

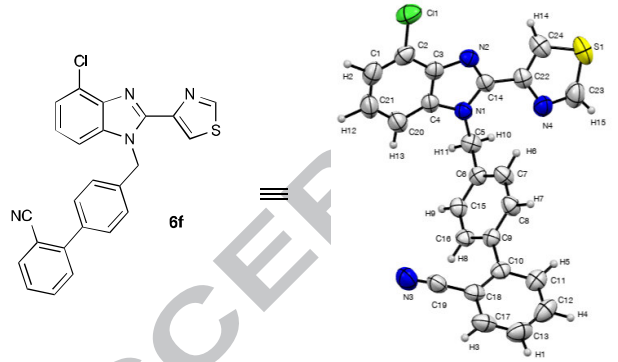
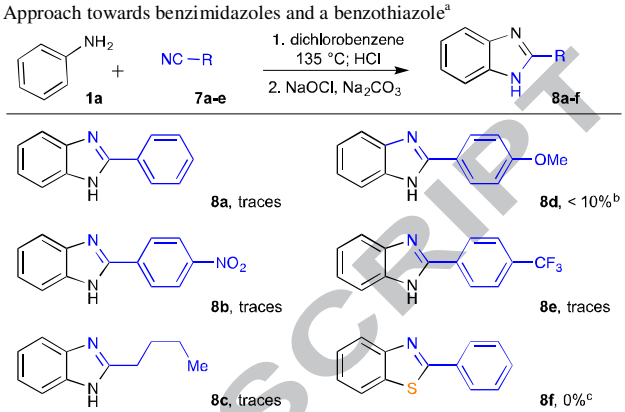


Figure 2. ORTEP representation of the X-ray crystal structure of **6f** showing atom labeling. 50% probability amplitude displacement ellipsoids are shown.[20]

Having optimized the reaction conditions for the synthesis of chlorinated thiabendazoles (Tables 1 and 2). It was suggested that other aromatic and aliphatic nitriles should be compatible to the reaction conditions (Table 3). In order to support of refuse this hypothesis, we first reacted aniline **1a** and benzonitrile **7a** under the standard reaction conditions. We were surprise to observe only traces of the final 2-phenyl benzimidazole **8a**[21] adduct. However, we decided to continue our study using other aromatic nitriles, both electron-rich and electron-poor. The electron-rich 4-methoxybenzonitrile substrate afforded the expected product **8d**,[21] albeit in only 10% yield. For the electron-poor (4-CF_3, 4-NO_2) benzonitriles, only traces were observed again.[22] Unfortunately, the same outcome was experienced when the aliphatic nitrile (*n*-butyronitrile) was employed as starting material.[23] To complete this study, the synthesis of 2-phenyl benzothiazole[24] **8f** was attempted using benzonitrile and thiophenol. Unfortunately, not even the phenyl benzimidothioate salt of step 1 was observed (Table 3).

Table 3.
Approach towards benzimidazoles and a benzothiazole[a]



[a]Reaction conditions for step 1. Solvent = 1,2-dichlorobenzene, temp = 135 °C, aniline (**1a**) (49 mmol), nitrile (**7**) (45 mmol), then dry HCl. Step 2. Solvent: methanol/water 1:1, all amidine hydrochloride obtained (1 equiv), sodium carbonate (1 equiv), NaOCl (1 equiv).
[b]Yield of product calculated by ^1H and ^{13}C NMR.
[c]Thiophenol was used instead of aniline.

In conclusion, we have developed a simple and complementary method for the synthesis of several miscellaneous thiabendazoles from inexpensive starting materials and reagents. The significant advantages of this methodology are simplicity of operation, cost effectiveness, easy availability of starting materials and metal-free condition, with moderate to good yields of products. Hence, this approach is an attractive method for the synthesis of different types of substituted thiabendazoles for both academia and industrial settings. Regrettably, the reported conditions are not compatible with other aromatic or aliphatic nitriles, as well as, thiophenol.

Acknowledgements

The University of Texas at Arlington and the UTA Research Enhancement Program, partially financed this project. The authors also acknowledge Dr. Delphine Gout for X-ray data collection and the NSF grants (CHE-0234811 and CHE-0840509) for additional instrumentation. The authors also thank DST-Nanomission, India (SR/NM/NS-20/2014), DST-SERB, India (SERB/F/7013/2015-16) and Jain University, India for financial support. Antimicrobial screening was performed by CO-ADD (The Community for Antimicrobial Drug Discovery), funded by the Wellcome Trust (UK) and The University of Queensland (Australia).

Supplementary Material

Supplementary data [experimental procedures, ^1H, ^{13}C NMR data of all the compounds (**6a-m**), crystallographic data for (**6f**), and bioassays details] associated with this article can be found, in the online version, at http://

References

1. Moss, G. P.; Smith, P. A. S.; Tavernier, D., *Pure Appl. Chem.* **1995**, *67*, 1307.
2. (a) Katritzky, A. R., *Chem. Rev.* **2004,** *104* (5), 2125-2126. (b) Andrei, Y., *Chem. Rev.* **2014,** *114* (16), 7783-7783.

3. (a) Gaillard, S.; Cazin, C. S. J.; Nolan, S. P. *Acc. Chem. Res.* **2012,** *45*, 778-787. (b) Peris, E. *Chem. Rev.* **2017**, *117*, ASAP.
4. (a) Hegedus, L. S. *J. Am. Chem. Soc.* **2009,** *131*, 17995-17997. (b) Patil, S.; Bugarin, A. *Eur. J. Org. Chem.* **2016,** *2016*, 860-870. (c) Patil, S.; White, K.; Bugarin, A. *Tetrahedron Lett.* **2014,** *55*, 4826-4829.
5. (a) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988,** *110*, 7188-7194. (b) Lamberth, C.; Dinges, J., Bioactive Heterocyclic Compounds Classes: Agrochemicals. Wiley-VCH Verlag GmbH & Co. KGaA: **2012**.
6. (a) Hallett, J. P.; Welton, T. *Chem.Rev.* **2011,** *111*, 3508-3576. (b) Müller, H., Tetrahydrofuran. In *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA: **2000**.
7. (a) Salahuddin; Shaharyar, M.; Mazumder, A. *Arabian J. Chem.* **2017**, *10*, S157–S173. (b) Yurttas, L.; Özkay, Y.; Gençer, H. K.; Acar. U. *J. Chem.* **2015**, Article ID 464379, 7 pages.
8. Zhang, C.; Zhong, B.; Yang, S.; Pan, L.; Yu, S.; Li, Z.; Li, S.; Su, B.; Meng, X. *Bioorg. Med. Chem.* **2015**, *23*, 3774-3780.
9. (a) Nofal, Z. M.; Soliman, E. A.; Abd El-Karim, S. S.; El-Zahar, M. I.; Srour, A. M.; Sethumadhavan, S.; Timothy J. Maher, T. J. *J. Heterocyclic Chem.* **2014**,*51*, 1797-1806. (b) Özkay, Y.; Yurttas, L.; Dikmen, M.; Engur, S. *Med. Chem. Res.* 2016, *25*, 482-493. (c) Sharma, P.; Srinivasa Reddy, T.; Thummuri, D.; Senwar, K. R.; Praveen Kumar, N.; Naidu, V. G. M.; Bharghava, S. K.; Shankaraiah, N. *Eur. J. Med. Chem.* **2016**, *124*, 608-621.
10. (a) Siddiqui, H. L.; Rehman, M. Z.; Ahmad, N.; Weaver, G. W.; Lucas, P. D. *Chem. Pharm. Bull*. **2007**, *55*, 1014. (b) Elnima, E. I.; Uppal Zubair, M.; Al-Badr, A. A. *Antimicrob. Agents Chemother.* **1981**, 29-32. (c) Zhang, H.-Z.; He, S. C.; Peng, Y. J.; Zhang, H. J.; Gopala, L.; Tangadanchu, V. K. R.; Gan, L. L.; Zhou, C. H. *Eur. J. Med. Chem.* **2017**, *136*, 165-183. (d) Kankate, R. S.; Gide, P. S.; Belsare, D. P. *Arabian J. Chem.* **2015**, http://dx.doi.org/10.1016/j.arabjc.2015.02.002.
11. Upadhyay, M. P.; West, E. P.; Sharma, A. P. *Br. J. Ophthalmol.* **1980**, *64,* 30-32.
12. (a) Gudmundsson, K. S.; Freeman, G. A.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2000**, *43*, 2473-2478. (b) Kim, M.; Shin, H.; Park, K.; Kim, H.; Park, J.; Kim, K.; Nam, J.; Choo, H.; Chong, Y. *J. Med. Chem.* **2015**, *58*, 596–7602.
13. Brown, H. D.; Matzuk, A. R.; Harris, S. A.; Sarett, L. H.; Ecerton, J. R.; Yakstis, J. J.; Campbell, W. C.; Cuckler. Application made in United States of America (No. 124,771) on July 18, **1961**, 1,009,807.
14. Brown, H. D.; Matzuk, A. R.; Harris, S. A.; Sarett, L. H.; Ecerton, J. R.; Yakstis, J. J.; Campbell, W. C.; Cuckler, A. C. *J. Am. Chem. Soc.* **1961**, *83*, 1764–1765.
15. Hoff, D. R.; Fisher, M. H.; Bochis, J.; Lusl, A.; Waksmunski, F.; Egerton, J. R.; Yakstis, J. J.; Cuckler, A. C.; Campbell, W. C. *Experientia*, **1970**, 26, 550-51.
16. Grenda, V. J.; Jones, R. E.; Gal, G.; Sletzinger, M. *J. Org. Chem.* **1965**, *30*, 259–261.
17. *General procedure for the synthesis of thiabendazoles* (**4a-d**): To a solution of 4-cyanothiazole (5.0 g, 45.0 mmol) in *o*-dichlorobenzene (40.0 mL) was added the respective aniline (**1a-d**) (49.0 mmol). The reaction mixture was heated at 135 ºC with purging excess dry HCl for 3 h. Then, cooled the reaction mixture to 40 ºC and the resulting solids were filtered, washed with more *o*-dichlorobenzene (10.0 mL). The solids were dried at 90 ºC under vacuum to give amidine hydrochlorides adducts. Then, to (31.0 mmol) of amidine hydrochloride in water (35.0 mL) was added methanol (35.0 mL) at room temperature. Cooled the reaction mixture to 0-5 ºC, added sodium carbonate (3.4 g, 31.0 mmol) and stirred the reaction mixture for 20 minutes. To the reaction mixture was added NaOCl (31.0 mmol, 12% w/v) (1.9 mL) at 5-10 ºC. Then, the reaction mixture was heated to 60-65 ºC and stirred for 2 h. Water (25.0 mL) was added to the reaction mixture and extracted with EtOAc (100 mL). The organic layer was concentrated under reduce pressure to get crude thiabendazoles. Finally, the crude compounds were purified by column chromatography using 9:1 DCM/EtOAc, affording pure thiabendazoles (**4a-d**).
18. Baldwin, J. E. *J. Chem. Soc., Chem. Commun* .**1976**, 734-736.
19. Addition of NaI or use of alkyl bromides resulted on similar yields due to over-alkylation adducts.
20. For crystallography data of (**6f)** in CIF and other formats, see the supplementary data and the CCDC 1543602.
21. Lee, S.; Kim, Y.; Kumar, M. R.; Park, N.; Heo Y. *J. Org. Chem.* **2011**, *76*, 9577-9583.
22. Williams, J. M. J.; Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O. *Org. Lett.* **2009**, *11*, 2039-2042.
23. Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. *J. Org. Chem.*, **2008**, *73*, 7841-7844.
24. Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul. M. M. *J. Am. Chem. Soc.* **2011**, *132*, 3674-3675.

A Practical Method, NaOCl-Mediated, to Prepare Thiabendazoles via Intramolecular Amination Reaction

Vikrant Patil[a], Enrique Barragan[b], Shivaputra A. Patil[c], Siddappa A. Patil[a]*, Alejandro Bugarin[b]

HIGHLIGHTS:

1. A practical method for the synthesize several thiabendazole derivatives
2. A metal-free protocol is documented
3. Good functional group tolerance
4. Easy access to structurally complex heterocyles
5. Fully characterized adducts are reported