Preparation of benzofuran-2-carbohydrazide and its utilization for benzofuran-bearing 1,2,4-triazole and 1,3,4-oxadiazole synthesis

Ngo Thi Chau

Department of Pharmacy, Nguyen Tat Thanh University
ntchau@ntt.edu.vn

Abstract

Benzofuran, triazole and oxadiazole spontaneously occur in natural compounds with highly desired bioactivities, such as antibacterial, antifungal, antiviral and anticancer. These cyclic scaffolds happen in a variety of commercial medicines as well as developed drugs in late-stage clinical trials (eg. amiodarone, ramelteon, zibotentan, and ataluren). Benzofuran-bearing triazole and oxadiazole can be synthesized by click reaction, requiring an alkynyl group. The formation of the alkynyl group can be achieved by treating the precursor with sodium azide, a poisonous chemical that needs safe conditions for manipulation. In this study, a simple and convenient reflux-based method for the synthesis of benzofuran-involved triazole and oxadiazole was developed. Firstly, benzofuran-2-carbohydrazide (3) was prepared by the reaction of salicylaldehyde and ethyl chloroacetate, followed by the treatment with hydrazine hydrate. Subsequently, compound (3) reacted with KOH, CS2 and hydrazine hydrate to afford 4-amino-1,2,4-triazole-3-thiol derivative (4), existing in a tautomeric form with its thione isomer (4b) in 1:3 of molar ratio. Intriguingly, the reaction of (3) and 4-fluorobenzaldehyde afforded N'-(4-fluorobenzoyl)-1-benzofuran-2-carbohydrazide (6) instead of 1,3,4-oxadiazole derivatives. Their structures were confirmed by NMR and MS. Altogether, this study implies the potential of using the simple and cost-effective reflux-based method for benzofuran-bearing triazole and oxadiazole synthesis.

Received 18/05/2023
Accepted 13/06/2023
Published 31/07/2023

Keywords
Benzofuran, 4-amino-1,2,4-triazole-3-thiol, tautomer, 1,3,4-oxadiazole

1 Introduction

Benzofuran is a core unit spontaneously occurring in natural compounds that consist of interesting biological properties, such as antifungal [1, 2], antibacterial [3], anti-inflammatory, antiviral and anticancer [4]. Benzofuran also finds a wide range of applications in drug delivery (eg. fluorescent sensors, oxidants) [5], chemistry and agriculture [6]. Despite the possession of potent bioactivities, benzofuran is easily cleaved by natural oxidative and reductive conditions as well as polymerized in the presence of mineral acids [7]. Alternatively, C2 and C3-substituted benzofurans are much more stable and, thus, are being used as precursors for further study.

Carbohydrazide is relatively described as a useful building block for heterocyclic chemical syntheses, such as triazole and oxadiazoles, that exhibit interesting inhibition activities toward tumor cells [8], viral [9], and bacterial growth [10]. Besides, triazoles and oxadiazoles are core structural scaffolds for several drugs and pharmaceutical agents. Their derivatives possess antiparasitic, antidiabetic, anti-inflammatory, anticancer and antiviral properties [11, 12]. Furthermore, they are classified as major metal-free fungicides in wood protection [13, 14]. Triazoles and oxadiazole can be synthesized *via* cycloaddition methods, which require the precursors with isocyanate or cyanide groups, metal-based catalysts and strict conditions [15-17]. Alternatively, these heterocyclic compounds can be solvent-free microwave-assisted prepared but might need the addition of complicated matrix metal-based catalysts and material (eg. $PdCl_2(PPh_3)$/CuI/Et_3N/THF [18], $CeCl_3$/NaI/I_2/CH_3CN

[19], P_4S_{10}/Silica-gel [20]). Furthermore, benzofuran-bearing triazole and oxadiazole synthesis mostly replies to the Click reaction [21], which requires substances with the alkynyl group and sodium azide as a catalyst, which is high toxicity. Altogether, the methods for triazole and oxadiazole preparation are laborious and costly.

In this study, the synthesis of benzofuran-bearing 1,2,4-triazole and 1,3,4-oxadiazole using the simple and cost-effective reflux method was developed. Salicylaldehyde (1) was first refluxed with ethyl chloroacetate to produce ethyl benzofuran-2-carboxylate (2), followed by hydrazination that resulted in the formation of benzofuran-2-carboxylate (3). Subsequently, the reaction of (3) with carbon disulfide and hydrazine produced 4-amino-5-(benzofuran-2-yl)-1,2,4-triazole-3-thiol (4). The reaction of (3) with 4-fluorobenzaldehyde was expected to afford 1-(5-(benzofuran-2-yl)-2-(4-fluorophenyl)-1,3,4-oxadiazol-3(*2H*)-yl)ethan-1-one (5), but intriguingly, *N'*-(4-fluorobenzoyl)-1-benzofuran-2-carbohydrazide (6) was obtained, which might be contributed to the fluor substituent on benzyl scaffold. Altogether, our work demonstrates the possibility of synthesizing benzofuran-involved heterocyclic chemicals by the simple method using safer and cost-effective chemicals and can contribute as a good reference for further studies.

2 Experimental

General procedures: all chemicals and solvents were purchased from commercial sources and utilized without any further purification. NMR spectra were recorded on a spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C-NMR) using DMSO-*d6* as a solvent, and HR-ESI-MS was taken on a mass spectrometer.

Benzofuran-2-carbohydrazide was prepared as the previous description with a minor modification [22]. Briefly, 18.30 g (0.15 mole) salicylaldehyde (1) was stirred with 62.10 g potassium carbonate (0.45 mole) for half an hour. Subsequently, 18.38 g ethyl chloroacetate (0.15 mole) was added, and the reaction was heated to (80-90) ºC for 2 hours. The reaction solution was then poured into crushed ice, and extracted 3 times with 100 mL ethyl acetate (EA) each time. The organic layer was collected, and EA was dried out using a vacuum rotary evaporator leading to the formation of ethyl benzofuran-2-carboxylate (2) in liquid form, which was then used without further purification. 11.4 g (0.06 mole) compound (2) was heated with 18.0 g (0.18 mole) hydrazine solution under reflux for 4 hours. Subsequently, the reaction solution was cooled down and kept at 4 °C overnight to precipitate the product, which was recrystallized from 50 mL ethanol to form benzofuran-2-carbohydrazide (3) as white crystals with the isolated yield of 80 %. Its NMR and HRESIMS were as follows. ^{1}H-NMR (500 MHz, DMSO−d_6) δ (ppm), *J* (Hz): 10.02 (*s*, 1H), 7.76 (*dd*, *J* = 7.5, *J* = 0.75, 1H), 7.63 (*dd*, *J* = 7.5, *J* = 0.75, 1H), 7.51 (*d*, *J* = 0.5, 1H), 7.44 (*td*, *J* = 7.5, *J* = 0.75, 1H), 7.32 (*td*, *J* = 8.0, *J* = 0.75, 1H), 4.58 (*br*, 2H). ^{13}C-NMR (125 MHz, DMSO−d_6) δ (ppm): 157.8, 154.1, 148.4, 127.0, 126.6, 123.6, 122.6, 111.7, 108.7. HRESIMS calcd. for $C_9H_8O_2N_2[M+H]^+$ 177.0664, found 177.0722.

Preparation of 4-amino-5-(benzofuran-2-yl)-1,2,4-triazole-3-thiol (4a): 1.76 g compound (0.01 mole) (3) and 0.56 g (0.01 mole) KOH were dissolved in ethanol followed by drop-by-drop addition of 0.76 g (0.01 mole) CS_2. The reaction was stirred for 30 mins to form an intermediate thiocarbohydrazide that was subsequently washed 3 times with 50 mL diethyl ether for each time, dried and mixed with 2.5 mL (0.02 mole) hydrazine solution for 4-hour reflux. The complete reaction was cooled to room temperature (RT) and pH was adjusted to ~ 6 to 8 to precipitate the product, followed by recrystallization from 20 mL DMF:H_2O to give compound (4a).

White powder; isolated yield: 73 %; HRESIMS calcd. for $C_{10}H_8N_4OS$ $[M+H]^+$ 233.0492, found 233.0572.

4-Amino-5-(benzofuran-2-yl)-1,2,4-triazole-3-thiol (4a) ^{1}H-NMR (500 MHz, DMSO−d_6) δ (ppm), *J* (Hz): 7.81 (*d*, *J* = 7.75, 1H), 7.79 (*s*, 1H), 7.76 (*d*, J = 7.75, 1H), 7.53 (*t*, *J* = 7.75, 1H), 7.40 (*t*, *J* = 7.75, 1H) and 5.95 (*s*, 2H); ^{13}C-NMR (125 MHz, DMSO−d_6) δ (ppm): 177.2, 154.9, 153.6, 139.1, 127.5, 126.8, 124.3, 122.8, 111.9 and 110.8.

4-Amino-5-(benzofuran-2-yl)-2,4-dihydro-1,2,4-triazole-3-thione (4b) ^{1}H-NMR (500 MHz, DMSO−d_6) δ (ppm), *J* (Hz): 14.13 (*s*, 1H), 7.90 (*s*, 1H), 7.83 (*d*, *J* = 7.75, 1H), 7.71 (*d*, *J* = 7.75, 1H), 7.46 (*t*, *J* = 7.75, 1H), 7.35 (*t*, *J* = 7.75, 1H) and 5.95 (*s*, 2H); ^{13}C-NMR (125 MHz, DMSO−d_6) δ (ppm): 167.1, 154.0, 142.6, 141.4, 127.1, 126.6, 123.8, 122.5, 111.5 and 109.9.

Preparation of *N'*-(4-fluorobenzoyl)-1-benzofuran-2-carbohydrazide (6): 1.76 g (0.01 mole) compound (3) and 1.24 g (0.01 mole) 4-fluorobenzaldehyde were dissolved completely in 10 mL acetic anhydride and refluxed for 4 hours. The reaction solution was then cooled down to RT and poured into a beaker with ice cubes to precipitate the product, followed by recrystallization from 20 mL ethanol to obtain compound (6).

Light yellow powder, isolated yield: 67 %; ^{1}H-NMR (500 MHz, DMSO−d_6) δ (ppm), *J* (Hz): 10.54 (*s*, 1H), 9.95 (*s*, 1H), 7.80 (*d*, *J* = 7.5, 1H), 7.68 (*d*, *J* = 7.5, 1H), 7.65 (*s*, 1H), 7.49 (*t*, *J* = 7.5, 1H), 7.35 (*t*, *J* = 7.5, 1H) and 1.93 (*s*, 3H); ^{13}C-NMR (125 MHz, DMSO−d_6) δ (ppm): 168.5, 157.4, 154.3, 147.4, 127.2, 126.8, 123.8, 122.9, 111.9, 110.4 and 20.6. HRESIMS calcd. for $C_{11}H_{10}N_2O_3$ $[M+Na]^+$ 241.0589, found 241.0608.

3 Result and discussion

Benzofuran, triazole and oxadiazole are all unique structures occurring in natural compounds with biological activities of interest. Several cyclic compounds with the combination of benzofuran and triazole or oxadiazole gave a significant production to plants, probably by strongly inhibiting protein synthesis of bacterial and fungal pathogens [23]. Besides, these combinations were also reported to suppress the tumor cell and the replication of the virus within the human body [24]. Despite the great activity, benzofuran-bearing triazole and oxadiazole were less studied, which might be attributed to the difficulty of their synthesis. For these chemical syntheses, most of the studies used Click reaction, requiring alkynyl-involved precursors and highly poisonous chemicals, such as sodium azide [21], which is unconventional. Alternatively, these heterocyclic substances could be prepared using a microwave. However, microwave-assisted synthesis required complicated catalysts and supplements while having a low yield, thus, compromising the application of these methods [18-20]. Meanwhile, carbohydrazide can be a potential intermediate for oxadiazole and triazole preparation with the use of cost-effective and simple methods, including reflux and acid/base catalyst.

To evaluate the possibility of benzofuran-involved triazole and oxadiazole synthesis using carbohydrazide as the precursor, benzofuran-2-carbohydrazide (3) was first prepared from salicylaldehyde (1), ethyl chloroacetate and hydrazine hydrate. The reaction of compound (3) with CS_2, KOH and hydrazine hydrate successfully yielded 4-amino-5-(benzofuran-2-yl)-1,2,4-triazole-3-thiol (4a) (Scheme 1). Very interestingly, its ^{1}H and ^{13}C-NMR spectra showed pairs of signals with the integrated intensity of 1:3, suggesting the existence of 4a with its isomer 4-amino-5-(benzofuran-2-yl)-2,4-dihydro-1,2,4-triazole-3-thione (4b) (Scheme 2). The synthesis of other 4-aminol-1,2,4-triazole-5-thiol derivatives mostly existed in thiol form, due to higher stability. However, in this case, thione (4b) occupied 75 % of the molar ratio, indicating its higher stability than its counterpart, thiol (4a).

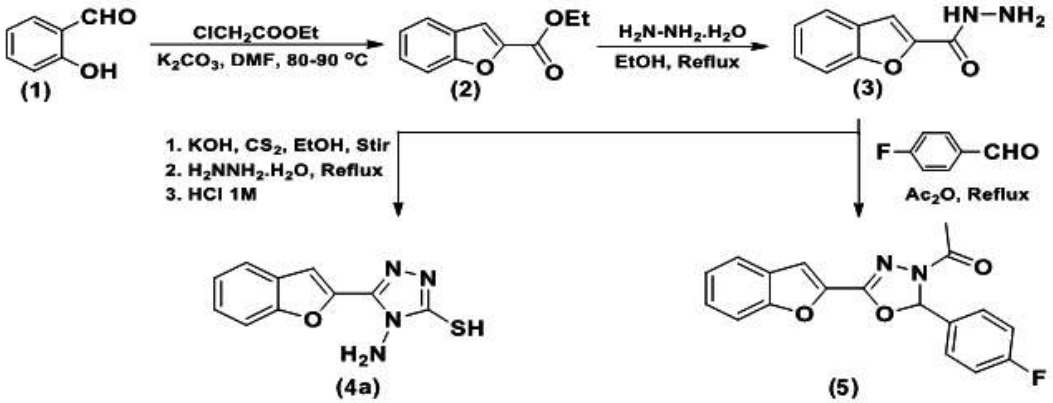
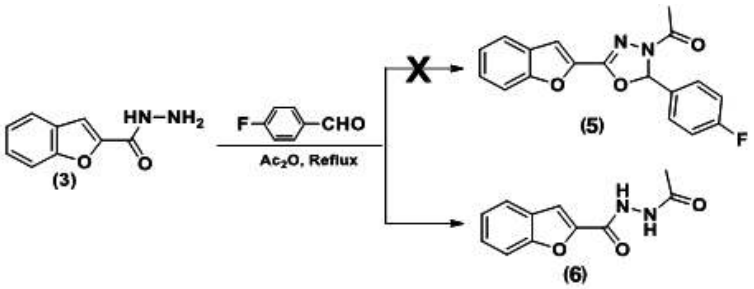


Fig. 1 Proposal pathway for preparation of benzofuran-bearing triazole and oxadiazole

Fig. 2 Tautomeric transformation of 4-Amino-5-(benzofuran-2-yl)-1,2,4-triazole-3-thiol (4a) and 4-Amino-5-(benzofuran-2-yl)-2,4-dihydro-1,2,4-triazole-3-thione (4b)

Alternatively, the reaction of carbohydrazide with benzaldehyde derivatives in acetic anhydride gave *N'*-acetyl-1,3,4-oxadiazole derivatives [25]. Following the description from the literature, compound (3) was refluxed with 4-fluorobenzaldehyde, and the product was purified for further NMR analysis. Besides ^{1}H and ^{13}C signals of benzofuran, interestingly, 2 *singlet* signals on ^{1}H-NMR (δ_H 9.95 and 10.54) and 2 signals on ^{13}C-NMR (δ_C 168.5 and 157.4) were obtained, that could be attributed to hydrogen in carbohydrazide group −N**H**−N**H**− and carbon in two carbonyl groups, suggesting the formation of *N'*-(4-fluorobenzoyl)-1-benzofuran-2-carbohydrazide (6) instead of 1-(5-(benzofuran-2-yl)-2-(4-fluorophenyl)-1,3,4-oxadiazol-3(*2H*)-yl)ethan-1-one (5) (Scheme 3). This interesting phenomenon might be attributed to the fluoro group. According to the literature, the formation of 1,3,4-oxadiazole from carbohydrazide and benzaldehyde derivatives occurs *via* 2 steps, including the condensation of $-NH_2$ and −CHO to form −N=CH−, and cyclization of 1,3,4-oxadiazole, probably by the interaction of =CH− and −CO− supported by acetic anhydride [26]. In the case of 4-fluorobenzaldehyde, fluoro substituent with extremely high electronegativity raised a negative effect on the latter step of 1,3,4-oxadiazole cyclization, apparently due to the interference of =CH− and −CO− interaction, leading to the break of −N=CH− during the cyclic arrangement and thus, forming compound (5) instead. This observation highlights the importance of the substituent group and maybe position on 1,3,4-oxadiazole formation in the reaction of carbohydrazide and benzaldehyde.



Scheme 3 Formation of *N'*-acetybenzofuran-2-carbohydrazide (6) instead of 1,3,4-oxadiazole derivative (5)

Nowadays, more and more studies on the discovery of new natural and synthetic benzofuran, triazole, and oxadiazole with extremely biological properties. Some of them have been utilized as drug and pharmaceutical agents, while others have been on clinical trial for human use. Their combination can be a new class for organic synthesis and drug development. This study established a simple and convenient reflux-based method for preparation of benzofuran-bearing triazole and oxadiazole, that can be used for subsequent tests of biological activity. Furthermore, the synthesized triazole (4a) with two active groups, amino and thiol, could be used as the precursor for further heterocyclic syntheses, such as thiadiazepines, thiazines, tetrazines and thiol-carbonyl derivatives. This study, generally, can be a good reference for further study and analysis.

4 Conclusion

In this study, a simple and efficient reflux method was developed for the synthesis of benzofuran-involved 1,3,4-triazole, which was found to be in a tautomeric form of thiol and thione with the molar ratio of 1:3. The reaction of benzofuran-2-carbohydrazide and 4-fluorobenzaldehyde was discovered not to form oxadiazole, but intriguingly afford *N'*-(4-fluorobenzoyl)-1-benzofuran-2-carbohydrazide, which

can be attributed to the fluor substituent. All the synthesized chemical structures were confirmed by NMR and MS. Altogether, the study establishes a convenient synthetic method for benzofuran-bearing oxadiazole and triazole with highly applicable in the laboratory and no use of toxic chemicals such as sodium azide. Moreover, the study can be a good literature for further research in synthesizing benzofuran-involved triazole and oxadiazole.

For further study, the mixture of (4a) and (4b) can be used as the precursor for the preparation of thiadiazepine and thiadiazine, as well as their anticancer and antiviral activities to be evaluated.

References

1.Aslam, S. N., Stevenson, P. C., Phythian, S. J., Veitch, N. C., & Hall, D. R. (2006). *Synthesis of cicerfuran, an antifungal benzofuran, and some related analogues*. Tetrahedron, 62(17), 4214-4226.

2. Masubuchi, M., Ebiike, H., Kawasaki, K.-i., Sogabe, S., Morikami, K., Shiratori, Y., Tsujii, S., Fujii, T., Sakata, K., & Hayase, M. (2003). *Synthesis and biological activities of benzofuran antifungal agents targeting fungal N-myristoyltransferase*. Bioorganic & Medicinal Chemistry, 11(20), 4463-4478.

3. Xu, Z., Zhao, S., Lv, Z., Feng, L., Wang, Y., Zhang, F., Bai, L., & Deng, J. (2019). *Benzofuran derivatives and their anti-tubercular, anti-bacterial activities.* European Journal of Medicinal Chemistry, 162, 266-276.

4. Galal, S. A., Abd El-All, A. S., Abdallah, M. M., & El-Diwani, H. I. (2009). *Synthesis of potent antitumor and antiviral benzofuran derivatives.* Bioorganic & Medicinal Chemistry Letters, 19(9), 2420-2428.

5. Abbas, A. A., & Dawood, K. M. (2023). *Anticancer therapeutic potential of benzofuran scaffolds*. RSC Advances, 13(16), 11096-11120.

6. Kumar, A., Rasool, J., & Ahmed, Q. N. (2022). Chapter 3 − Applications of 2-Oxoaldehydes. In A. Kumar, J. Rasool, & Q. N. Ahmed (Eds.), Chemistry of 2-Oxoaldehydes and 2-Oxoacids (pp. 63-171). *Elsevier.*

7. Walter, D. S. (1995). 3.06 - Ketones Bearing an α,β-Aryl or -Hetaryl Substituent. In A. R. Katritzky, O. Meth-Cohn, & C. W. Rees (Eds.), Comprehensive Organic Functional Group Transformations (pp. 277-312). *Elsevier Science.*

8. Barbosa, V. A., Formagio, A. S. N., Savariz, F. C., Foglio, M. A., Spindola, H. M., de Carvalho, J. E., Meyer, E., & Sarragiotto, M. H. (2011). *Synthesis and antitumor activity of β-carboline 3-(substituted-carbohydrazide) derivatives.* Bioorganic & Medicinal Chemistry, 19(21), 6400-6408.

9. Al-Wahaibi, L. H., Abdalla, M., Mary, Y. S., Mary, Y. S., Costa, R. A., Rana, M., El-Emam, A. A., Hassan, H. M., & Al-Shaalan, N. H. (2022). *Spectroscopic, Solvation Effects and MD Simulation of an Adamantane-Carbohydrazide Derivative, a Potential Antiviral Agent.* Polycyclic Aromatic Compounds, 1-15.

10. Pieczonka, A. M., Strzelczyk, A., Sadowska, B., Mlostoń, G., & Stączek, P. (2013). *Synthesis and evaluation of antimicrobial activity of hydrazones derived from 3-oxido-1H-imidazole-4-carbohydrazides.* European Journal of Medicinal Chemistry, 64, 389-395.

11. Sathish Kumar, S., & P Kavitha, H. (2013). *Synthesis and biological applications of triazole derivatives–a review.* Mini-Reviews in Organic Chemistry, 10(1), 40-65.

12. Vaidya, A., Jain, S., Jain, P., Jain, P., Tiwari, N., Jain, R., Jain, R., K Jain, A., & K Agrawal, R. (2016). *Synthesis and biological activities of oxadiazole derivatives: A review.* Mini Reviews in Medicinal Chemistry, 16(10), 825-845.

13. Cui, Z.-N., Shi, Y.-X., Zhang, L., Ling, Y., Li, B.-J., Nishida, Y., & Yang, X.-L. (2012). *Synthesis and fungicidal activity of novel 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives.* Journal of Agricultural and Food Chemistry, 60(47), 11649-11656.

14. Abedinifar, F., Farnia, S. M. F., Hosseinihashemi, S. K., Jalaligoldeh, A., Arabahmadi, S., & Mahdavi, M. (2020). *Design and synthesis of new benzofuran-1, 2, 3-triazole hybrid preservatives and the evaluation of their antifungal potential against white and brown-rot fungi.* Bioresources, 15(4), 7828.
15. Matheau-Raven, D., & Dixon, D. J. (2022). *A One-Pot Synthesis-Functionalization Strategy for Streamlined Access to 2,5-Disubstituted 1,3,4-Oxadiazoles from Carboxylic Acids.* The Journal of Organic Chemistry, 87(18), 12498-12505.
16. Mohammadi, B., & Adib, M. (2014). *Microwave assisted one-pot tandem three-component synthesis of 2,4,5-triary1-2-4-dihydro-3H-1,2,4-triazol-3-one derivatives.* Chinese Chemical Letters, 25(4), 553-556.
17. Wei, Q., Qiao, C., Xia, Z., & Chen, S. (2013). Efficient in Situ Synthesis of 3,5-Disubstituted-1,2,4-triazoles Under Microwave-Assisted Conditions. Synthetic Communications, 43(23), 3181-3191.
18. Willy, B., Rominger, F., & Müller, T. J. J. (2008). *Novel Microwave-Assisted One-Pot Synthesis of Isoxazoles by a Three-Component Coupling-Cycloaddition Sequence.* Synthesis, 2008(02), 293-303.
19. Bartoli, G., Cimarelli, C., Cipolletti, R., Diomedi, S., Giovannini, R., Mari, M., Marsili, L., & Marcantoni, E. (2012). *Microwave-Assisted Cerium(III)-Promoted Cyclization of Propargyl Amides to Polysubstituted Oxazole Derivatives.* European Journal of Organic Chemistry, 2012(3), 630-636.
20. Gangal, S., Sharma, S., & Rauf, A. (2008). *Microwave-Assisted Synthesis of 2-Long Alkenyl Chain Benzoxazoles and Naphtho[2,3-d]oxazoles and Their Antimicrobial Evaluation.* Phosphorus, Sulfur, and Silicon and the Related Elements, 184(1), 242-259.
21. Xiong, X., & Cai, L. (2013). *Application of magnetic nanoparticle-supported CuBr: a highly efficient and reusable catalyst for the one-pot and scale-up synthesis of 1,2,3-triazoles under microwave-assisted conditions [10.1039/C3CY20680G].* Catalysis Science & Technology, 3(5), 1301-1307.
22. Parekh, S., Bhavsar, D., Savant, M., Thakrar, S., Bavishi, A., Parmar, M., Vala, H., Radadiya, A., Pandya, N., & Serly, J. (2011). *Synthesis of some novel benzofuran-2-yl (4, 5-dihyro-3, 5-substituted diphenylpyrazol-1-yl) methanones and studies on the antiproliferative effects and reversal of multidrug resistance of human MDR1-gene transfected mouse lymphoma cells in vitro.* European Journal of Medicinal Chemistry, 46(5), 1942-1948.
23. Faiz, S., Zahoor, A. F., Ajmal, M., Kamal, S., Ahmad, S., Abdelgawad, A. M., & Elnaggar, M. E. (2019). *Design, synthesis, antimicrobial evaluation, and laccase catalysis effect of novel benzofuran–oxadiazole and benzofuran-triazole hybrids.* Journal of Heterocyclic Chemistry, 56(10), 2839-2852.
24. Kharb, R., Shahar Yar, M., & Chander Sharma, P. (2011). *Recent advances and future perspectives of triazole analogs as promising antiviral agents*. Mini Reviews in Medicinal Chemistry, 11(1), 84-96.
25. Da, Y. X., Yang, Z., Quan, Z. J., Zhang, Z., & Wang, X. C. (2009). *Utilization of 2-benzo [b] furan carboxylic acid hydrazide in the synthesis of 1, 3, 4-oxadiazole derivatives.* Journal of Heterocyclic Chemistry, 46(4), 737-741.
26. Da, Y.-X., Yang, Z., Quan, Z.-J., Zhang, Z., & Wang, X.-C. (2009). *Utilization of 2-benzo[b]furan carboxylic acid hydrazide in the synthesis of 1,3,4-oxadiazole derivatives.* Journal of Heterocyclic Chemistry, 46(4), 737-741.

Điều chế benzofuran-2-carbohydrazide để tổng hợp benzofuran mang 1,2,4-triazole và 1,3,4-oxadiazole

Ngô Thị Châu

Khoa Dược, Đại học Nguyễn Tất Thành
ntchau@ntt.edu.vn

Tóm tắt Các dị vòng benzofuran, triazole and oxadiazole thường được tìm thấy trong các hợp chất tự nhiên với những hoạt tính sinh học quý báu như kháng khuẩn, kháng nấm, kháng vi rut và kháng ung thư. Những dị vòng này cũng thường xuất hiện rộng rãi trong các loại thuốc đang được sử dụng hằng ngày hoặc những loại thuốc quý đang được thử nghiệm lâm sàng giai đoạn cuối (thí dụ như amiodarone, ramelton, zibotentan, và ataluren). Các dẫn xuất triazole và oxadiazole chứa dị vòng benzofuran thường được tổng hợp thông qua phản ứng "Click" dựa trên nền chất có nhóm chức alkynyl. Tuy nhiên, tổng hợp chất nền với nhóm chức alkynyl thường dựa trên tác chất sodium azide, một hợp chất khá độc với con người và vì vậy đòi hỏi độ an toàn và điều kiện thí nghiệm khắc khe. Để giải quyết vấn đề này, phương pháp tổng hợp dẫn xuất triazole và oxadiazole chứa dị vòng benzofuran sử dụng dụng cụ đơn giản, tiết kiệm và hiệu quả được nghiên cứu và đánh giá. Hợp chất benzofuran-2-carbohydrazide (3) được tổng hợp bằng phản ứng của salicylaldehyde, ethyl chloroacetate và hydrazine. Sau đó, hợp chất (3) phản ứng với KOH, CS_2 và hydrazine tạo thành dẫn xuất 4-amino-1,2,4-triazole-3-thiol (4), tồn tại trong hợp hai isomers (thiol và thione) với tỉ lệ mole là 1:3. Phản ứng giữa hợp chất (3) và 4-fluorobenzaldehyde tạo thành dẫn xuất *N*′-(4-fluorobenzoyl)-1-benzofuran-2-carbohydrazide (6), thay vì 1,3,4-oxadiazole như mong đợi. Cấu trúc hoá học của các dẫn xuất tổng hợp trong bài được xác định bằng các phương pháp phổ hiện đại như NMR và MS. Công trình nghiên cứu này phát triển phương pháp tổng hợp dẫn xuất triazole and oxadiazole chứa dị vòng benzofuran một cách hiệu quả và tiết kiệm.

Từ khóa Benzofuran, 4-amino-1,2,4-triazole-3-thiol, tautomer, 1,3,4-oxadiazole