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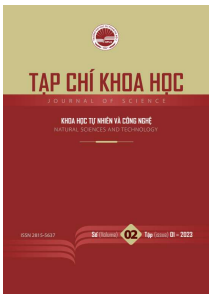

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Synthesis of new 1,2,4-triazine derivatives bearing the benzofuran moiety

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Abstract

In the aim of further research of the highly bioactive benzofuran and triazine derivatives, the synthesis of 1,2,4-triazine derivatives bearing the benzofuran moiety has been undertaken. Using a simple and convenient method, a three steps synthesis of novel functionalized 1,2,4-triazine derivatives from readily available starting materials has been described. Herein, two derivatives of 1,2,4-triazine were obtained in moderate yields. The structures of all synthesized compounds were elucidated by spectral methods of analysis

Keywords: Benzofuran, 1,2,4-triazine hybrid molecule.

1. Introduction

In recent years, hybrid molecules, the combination of two or more active agents in a single molecule, have been widely studied by many pharmaceutical research groups. Multiple projects have aimed to design and synthesis these compounds and the results are very encouraging. These hybrid molecules exhibit strongly biological potential such as anticancer, antituberculosis, anti-inflammatory, antibacterial, antifungal and antimalarial.[1]

Benzofuran moiety is widely occurred in natural compounds and has become attractive to researchers because of their biological activities including antifungal, antibacterial, antiviral, anticancer and anti-HIV activities.[2-4] In addition, 1,2,4-triazine derivatives have wide spectrum of biological activities, as diverse as antibacterial, antifungal, anti-inflammatory, antidepressant, antiviral, anticancer…[5] Synthesis and structural modification of 1,2,4-triazine to be able to explore different

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biological activities has now become an important goal of several research groups. However, due to the ability to create many different derivatives or combine with other frameworks, the research direction on synthesizing 1,2,4-triazine derivatives is still very promising and developing widely.

Therefore, the goal of this research is to prepare some novel hybrid molecules of 1,2,4-triazine derivatives bearing the benzofuran moiety. In the present study, the three steps synthesis starting from salicylaldehyde was achieved.

2. Materials and methods

2.1. General

All chemicals were purchased from Merck (for synthetic class) and Sigma Aldrich while organic solvents were purchased from the commercial source and were used without any further purification. The NMR spectra were acquired using the Bruker Avance III spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). Chemical shifts are expressed in parts per million (ppm) and reported relative to the residual solvent signal as an internal reference. High resolution mass spectra (HRMS) were recorded using a HRMS X500$_R$ QTOF mass spectrometer in electrospray ionization (ESI) mode. The melting points were determined using a Gallenkamp digital Melting point apparatus 5A-6797 with a rate of heating of 2°C/min. Reactions were monitored using thin layer chromatography (TLC) on silica gel plates (silica gel 60 F_{254}, Merck), visualized under ultraviolet light (254 nm). Column chromatography was performed on silica gel Merck 60 (230–400 mesh) purchased from HiMedia Laboratories Pvt. Ltd. (India).

*2.2. Synthesis of ethyl benzofuran-2-carboxylate (**1**)*

A solution of salicylaldehyde (18.30 g, 0.15 mol) and potassium carbonate (62.10 g, 0.45 mol) in DMF (150 mL) was stirred at room temperature for 30 minutes. Then, ethyl chloroacetate (18.38 g, 0.15 mol) was slowly dropped into that solution while the mixture was stirred during two hours at 80–90 °C. The color of solution was changed from yellow to green, dark green, brown and finally black. Consequently, that solution was poured into crushed ice and was extracted with ethyl acetate (100 mL × 3). Then, the combined organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford ethyl benzofuran-2-carboxylate **(1)** (21.9 g, 77%).

Dark yellow liquid; ^{1}H–NMR (500 MHz, DMSO-d_6): δ_H (ppm): 7.75 (*dd*, *J* = 7.9 Hz, 1.2, 1H), 7.67 (*dd*, *J* = 8.4, 1.2 Hz, 1H), 7.65 (*s*, 1H), 7.47 *(ddd*, *J* = 8.4, 7.3, 1.2 Hz, 1H), 7.31(*ddd*, *J* = 7.9, 7.3, 1.2 Hz, 1H), 4.32 (*q*, *J* = 7.0 Hz, 2H), 1.30 (*t*, *J* = 7.0 Hz, 3H); ^{13}C–NMR (125 MHz, DMSO-d_6): δ_C (ppm): 158.6, 155.0, 145.1, 127.7, 126.6, 123.8, 123.0, 113.8, 112.0, 61.1, 13.9. These data are consistent with that reported in the literature.[6]

*2.3. Synthesis of benzofuran-2-carbohydrazide (**2**)*

A solution of ethyl benzofuran-2-carboxylate **(1)** (11.40 g, 0.06 mol) in absolute ethanol (30 mL) was slowly continuously added by hydrazine hydrate 50% (18.00 g, 0.18 mol) under reflux for four hours. Upon completion, the reaction mixture was kept at 2–4 °C overnight to solidify the product. Consequently, the separated solid was filtered, washed with cold ethanol and then recrystallized in absolute ethanol to give benzofuran-2-carbohydrazide **(2)** (8.46 g, 80%).

White crystals, melting point 190–194 °C (lit. [6] 190–194 °C); ^{1}H–NMR (500 MHz, DMSO-d_6): δ_H (ppm): 10.02 (*s*, 1H), 7.76 (*dd*, *J* = 8.0, 0.8 Hz, 1H), 7.63 (*dd*, *J* = 8.4, 0.8 Hz, 1H), 7.51 (*s*, 1H), 7.44 (*ddd*, *J* = 8.4, 7.3, 0.8 Hz, 1H), 7.32 (*ddd*, *J* = 8.0, 7.3, 0.8 Hz, 1H), 4.58 (*br,* 2H); ^{13}C–NMR

(125 MHz, DMSO-d_6): δ_C (ppm): 157.8, 154.1, 148.4, 127.0, 126.6, 123.6, 122.6, 111.7, 108.7. These data are consistent with that reported in the literature.[6]

*2.4. General procedure for the synthesis of phenacyl bromide compounds (**3**)*

A solution of acetophenone derivative (10 mmol) in chloroform (10 mL) at 0 °C was added by few drops of H_2SO_4. Then, a cold chloroform solution of bromine (1.6 g, 10 mmol) was dropwise added. That system was kept stirring at the same temperature for half an hour and then at room temperature for another hour. Consequently, a solution $Na_2S_2O_3$ 10% (20 mL) was added to the mixture. The aqueous phase was extracted with chloroform (20 mL × 3). All organic phases were collected, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was purified by recrystallization in EtOH to give the corresponding product.

2-bromo-1-phenylethan-1-one (**3a**): 1.78 g, yield: 90%, white needle crystals; ^{1}H-NMR (500 MHz, $CHCl_3$) δ_H (ppm): 7.99 (*dd*, *J* = 8.3, 1.4 Hz, 2H), 7.61 (*td*, *J* = 7.3, 1.4 Hz, 1H), 7.52 – 7.47 (*m*, 2H), 4.46 (*s*, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C (ppm): 191.4, 134.1, 133.9, 129.1, 129.0, 31.1, 31.0.

2-bromo-1-(4-chlorophenyl)ethan-1-one (**3b**): 1.98 g, yield: 85%, white needle crystals; ^{1}H-NMR (500 MHz, $CHCl_3$) δ_H (ppm): 7.93 (*d*, *J* = 8.6 Hz, 2H), 7.47 (*d*, *J* = 8.6 Hz, 2H), 4.41 (*s*, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C (ppm): 190.4, 140.7, 132.4, 130.5, 129.4, 30.5.

2.5. General procedure for the synthesis of 3-(benzofuran-2-yl)-6-aryl-1,2,4-triazine (4)

Dissolve benzofuran-2-carbohydrazide (**2**) (0.2 g, 1 mmol), sodium acetate (0.07 g, 0.8 mmol) and phenacyl bromide (**3**) (0.1 g, 0.5 mmol) in 10 mL of EtOH/CH_3COOH (v/v 3:1) and heat under reflux for for 12 hours. Then the reaction solution was cooled to room temperature. The solid obtained was filtered and washed with EtOH to obtain a yellow solid.

3-(benzofuran-2-yl)-6-phenyl-1,2,4-triazine (**4a**): 150 mg, yield: 55%, yellow needle crystals; ^{1}H-NMR (500 MHz, $CHCl_3$) δ_H (ppm): 9.07 (*s*, 1H), 8.20 – 8.14 (*m*, 2H), 7.94 (*d*, *J* = 1.0 Hz, 1H), 7.75 (*dd*, *J* = 7.8, 1.0 Hz, 1H), 7.69 (*dd*, *J* = 8.3, 0.9 Hz, 1H), 7.63 – 7.54 (*m*, 3H), 7.45 (*ddd*, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.34 (*ddd*, *J* = 8.0, 7.2, 0.9 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_H (ppm):157.0, 156.5, 155.2, 151.1, 146.5, 133.2, 131.3, 129.6, 128.3, 127.1, 126.9, 123.9, 122.6, 112.4, 111.3; HR-MS (TOF) calcd. for $C_{17}H_{11}ON_3$ $[M+H]^+$: 274.0975, found: 274.0962.

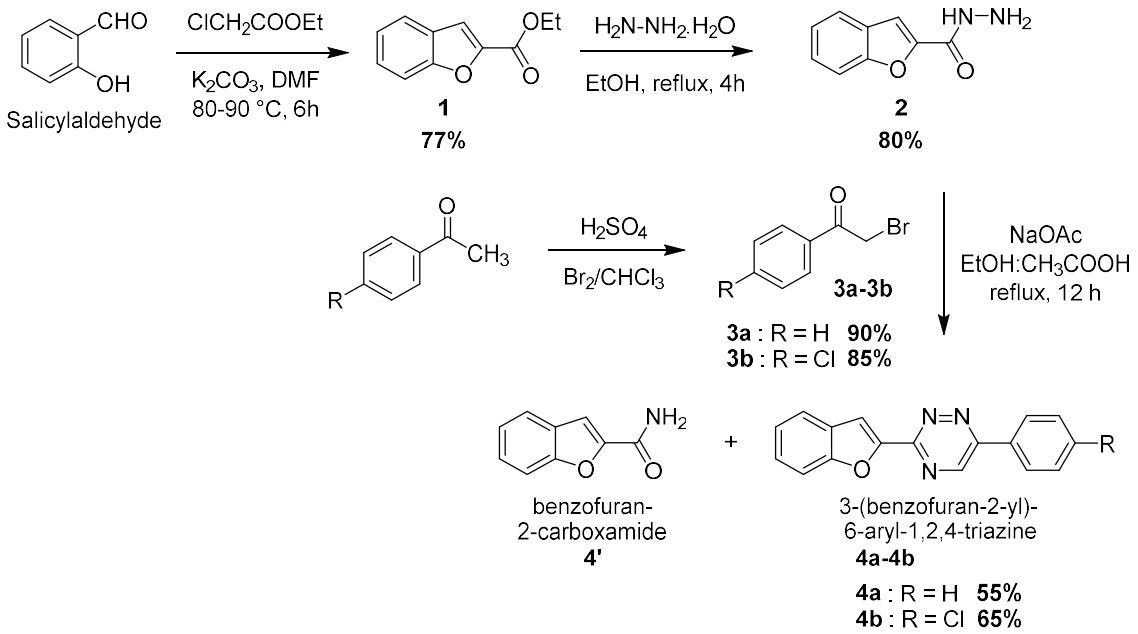
3-(benzofuran-2-yl)-6-(4-chlorophenyl)-1,2,4-triazine (**4b**): 199 mg, yield: 65%; yellow powder; ^{1}H-NMR (500 MHz, $CHCl_3$) δ_H (ppm): 9.05 (*s*, 1H), 8.12 (*d*, *J* = 8.6 Hz, 2H), 7.94 (*s*, 1H), 7.75 (*d*, *J* = 7.8 Hz, 1H), 7.69 (*d*, *J* = 8.3 Hz, 1H), 7.57 (*d*, *J* = 8.5 Hz, 2H), 7.45 (*ddd*, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.34 (*dd*, *J* = 7.8, 7.2 Hz, 1H); ^{13}C- NMR (125 MHz, $CDCl_3$) δ_H (ppm): 157.4, 156.8, 154.4, 151.2, 146.4, 138.1, 131.8, 130.2, 128.5, 128.4, 127.5, 124.2, 122.9, 112.7, 111.8; HR-MS (TOF) calcd. for $C_{17}H_{10}ON_3{}^{35}Cl$ $[M+H]^+$: 308.0585, found: 308.0572.

Benzofuan-2-carboxamide (**4'**): ^{1}H-NMR (500 MHz, $CHCl_3$) δ_H (ppm): 9.32 (*s*, 1H), 8.86 (*s*, 1H), 7.67 (*d*, *J* = 7.8 Hz, 1H), 7.52 (*m*, 2H), 7.45 (*t*, *J* = 7.5 Hz, 1H), 7.31 (*t*, *J* = 7.5 Hz, 1H); ^{13}C- NMR (125 MHz, $CDCl_3$) δ_H (ppm): 167.2, 155.0, 146.2, 127.6, 127.1, 124.0, 122.8, 112.2, 112.0.

3. Results and discussion

The 1,2,4-triazine (**4a, 4b**) derivatives were synthesized according to **Scheme 1**. Salicylaldehyde reacts with ethyl chloroacetate formed ethyl benzofuran-2-carboxylate (**1**), which was subsequently treated with hydrazine hydrate to afford benzofuran-2-carbohydrazide (**2**), with the yields of 77% and 80%, respectively. On the other hand, we prepared phenacyl bromide derivatives **3a** and **3b** by the

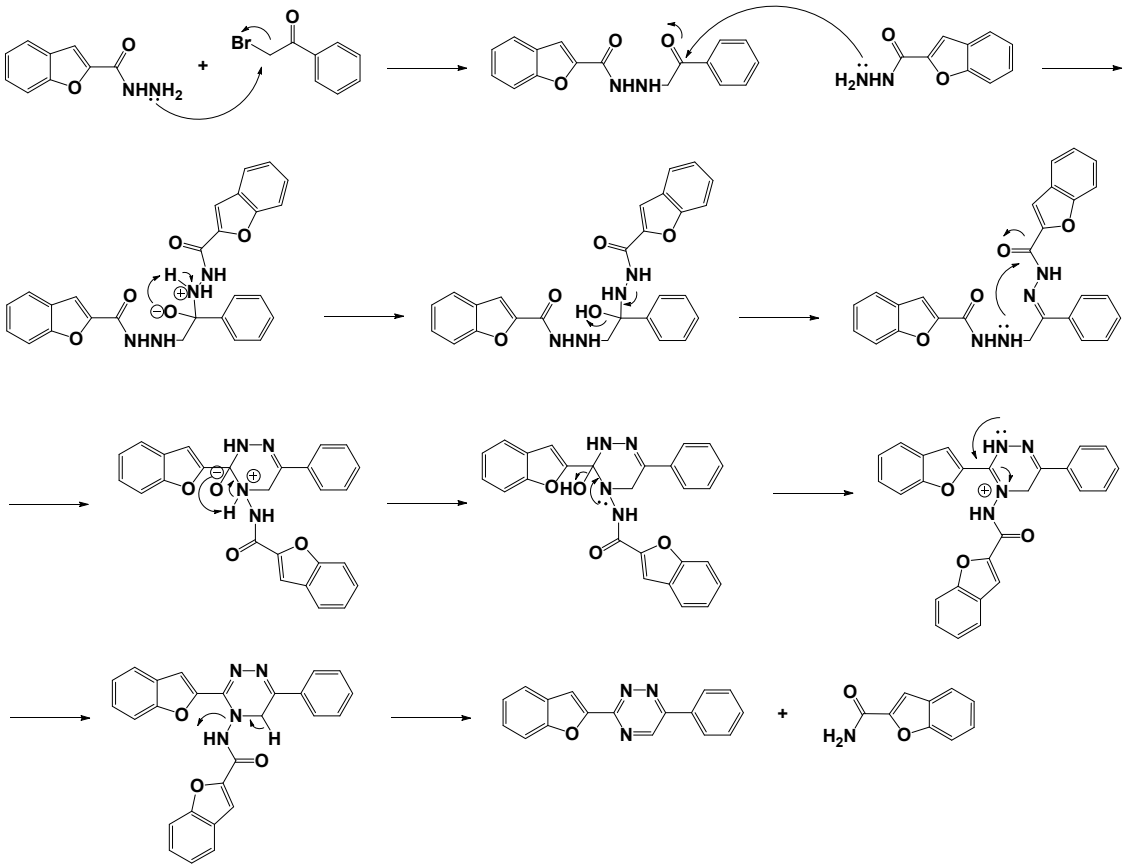
bromination of corresponding acetophenone compounds with the yields ranging from good to excellent.



Scheme 1. The synthetic route for the preparation of 1,2,4-triazine derivatives

The key step of this protocol is cyclization between benzofuran-2-carbohydrazide (**2**) and phenacyl bromide (**3**). We obtained two derivatives with moderate yields. The chemical structures of these products were elucidated using the ^{1}H and ^{13}C NMR spectra. The presence of *singlet* signal of proton N–C**H**=C at about 9.0-9.1 ppm and the disappearance of proton C**H**$_2$Br at 4.4 ppm in the ^{1}H–NMR spectrum of each derivative allowed us to confirm the successful cyclization. Furthermore, in the ^{13}C-NMR spectra, the disappearance of carbon **C**H$_2$Br at the high field signal about 30 ppm and of carbon **C**=O at about 190 ppm were further supportive of this structure.

A possible reaction mechanism for the formation of triazine has been proposed as shown in **Scheme 2**. First, the amino group of carbohydrazide attacks alpha carbon carbonyl by the S_N2 reaction. Then, the amino group of another carbohydrazide attacks the carbonyl group, followed by the dehydration to form imine compound. The cyclization reaction occurs between the amino group of the first carbohydrazide and carbonyl group of the second carbohydrazide, followed by dehydration and the leaving of benzofuan-2-carboxamide to form 1,2,4-triazine derivatives. We also isolated the benzofuan-2-carboxamide (**4'**), a by-product of this reaction. Its presence is evidence supporting the relevance of this mechanism.



Scheme 2. Proposed reaction mechanism of the formation of 1,2,4-triazine derivatives.

The obtained results can be explained by the effect of the substituent on the aromatic ring of phenacyl bromide. The mild electron withdrawing substituent (–Cl) which attract electrons to the aromatic ring can activate the carbonyl of phenacyl bromide. That leads to the formation of product **4b** with a higher yield (65%) compare to that of product **4a** (55%) in the absence of the substituent (R=H).

4. Conclusions

A facile, convenient and good yielding synthesis of novel 1,2,4-triazine derivatives bearing the benzofuran moiety from readily available starting materials has been described. Starting from salicylaldehyde, we have synthesized two 1,2,4-triazine derivatives in three steps. The product of the first step is ethyl benzofuran-2-carboxylate (**1**) with the yield of 77%. Then, the product (**1**) is converted to benzofuran-2-carbohydrazide (**2**) with the yield of 80%. The products of the third step are 1,2,4-triazine derivatives, namely, 3-(benzofuran-2-yl)-6-phenyl-1,2,4-triazine (**4a**) and 3-(benzofuran-2-yl)-6-(4-chlorophenyl)-1,2,4-triazine (**4b**) with the yields of 55% and 65%, respectively. As a result, the substituent on the aromatic ring showed an effect in the cyclization step. In fact, the substrate bearing a mild electron withdrawing group (–Cl) as substituent on the aromatic ring can lead to cyclization with a better yield. Their chemical structures were elucidated through NMR and HR–MS spectral analysis. All triazine derivatives are new compounds, reported for the first

time. The obtained products are the basis for further bioactivity testing for a promising application in drug development.

Declaration of Competing Interest

The authors declare no competing interests.

Author contributions

Que-Ngan Bui Thi performed the experiments and interpreted the NMR and MS data. Thu-Nghia Nguyen Thi and Thuy-Trang Nguyen Thien collected the bibliography and analyzed the experimental data of the synthesis. Tan Tai Nguyen designed the research, wrote the first draft, reviewed and edited the manuscript and supervised the investigation. All the authors have read and approved the content of the final manuscript.

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