SYNTHESIS OF 2-THIOPHENE CARBO HYDRAZIDES

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ABSTRACT
Carbohydrazides (carboxylic hydrazides) are typically made via hydrazinolysis of carboxylic acid esters in alcoholic solutions. Herein, we present a method for the synthesis of thiophene carbohydrazides with yields more than 90% and good purity via the chemical reaction of activated esters or amides with hydrazine. This novel technique was used to synthesis and analyze a variety of heteroaryl-, aryl-, and aralkyl-substituted carbohydrazides.

Keywords: Carbohydrazides, 2-thiophenecarboxylic hydrazide, 2-thenoyl-hydrazine, hydrogen bonding, thiophene carbohydrazide

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1.INTRODUCTION

An impressive feat in organic chemistry is the synthesis of 2-thiophene carbohydrazides. [1]Thiophene-based compounds' wide range of potential uses, from materials science to medicinal chemistry, has attracted a lot of research. The compound's distinctive structural characteristics and reactive potential are further expanded by the addition of carbohydrazide functionality. This synthesis is a multi-step procedure designed to add carbohydrazide moieties onto the 2-thiophene core in a selective and efficient manner. [2]Reactions like condensation and substitution may be a part of the approach, both of which need fine-tuning of reaction conditions to achieve high yields. [3]Nuclear magnetic resonance (NMR), Mass spectrometry (MS) and Infrared spectroscopy (IR), are three of the most important characterization methods for verifying the correctness of the produced compounds' identities and structures.

Both the structural uniqueness and the possible practical uses of these 2-thiophene carbohydrazides are of great importance. They may have biological activity of relevance for pharmacological study, or they may be used as adaptable building blocks in the production of innovative materials with customized features [4]. This synthesis is useful because it provides access to a new class of chemicals that has applications in a wide range of scientific fields.[5]

It is common practice to add a carbohydrazide group to molecules during the synthesis of organic and natural goods. The synthesis of other chemicals, such as hydrazones, Schiff bases, and coordination compounds, has piqued researchers' interest in hydrazides. [6] There are a number of methods available for preparing carbohydrazides at this time. To get the appropriate carbohydrazides, a simple technique includes making acyl anhydrides and acid chlorides, which then react quickly with hydrazine. However, acid chlorides and anhydrides are extremely reactive, making it challenging to halt the process once the monoacylation has been completed. To make carbohydrazides, one must first make the appropriate esters by reacting the respective acids with hydrazine. [7] Diacyl hydrazine is seldom produced in appreciable proportions by esters, however less reactive esters may need inconveniently prolonged reaction periods and/or severe reaction conditions. Solid-state hydrazinolysis of esters using hydroquinone and hydrazine inclusion complexes has also been described. Microwave irradiation and activated esters generated by catalytic coupling reagents are two more approaches, although neither is very effective for the direct manufacture of carbohydrazides from acids. [8] To that end, it is worthwhile to find a simple and effective approach of converting carboxylic acids into carbohydrazides.

2.LITERATURE REVIEW

Nabil Al-Zaqri (2020) In this work, we report the successful synthesis of thiophene-2-carbohydrazide, a new small-molecule amide tautomer, using microwave radiation (MW) conditions. DFT calculations at the B3LYP/6-311G(d,p) level of theory were used to model the prototrophic tautomerization of imidic thiophene-2- carbohydrazide through intramolecular proton migration. X-ray diffraction analysis confirmed the amide structure of the endo-isomer of thiophene-2-carboxyhydrazide, which is thought to be the kinetically preferred isomer. Parameters from the DFT structure were compared to their XRD experimental counterparts. Using the XRD-packing model, we were able to empirically discover several H-bond interactions inside the crystal lattice, which we subsequently connected with MEP and HSA calculations. Electronic characteristics such as border molecule orbital energies, absorbance, dipole moment, DOS, GRD quantum parameters, and TD-SCF/B3LYP were DFT estimated from experimental and theoretical data, respectively. Docking studies were performed using 1BNA DNA and the prototrophic (E)/(Z)-thiophene-2-carbohydrazonic acid tautomers of the thiophene-2-carbohydrazide isomers. The thermal behaviour and anticipated Ea-a relations were calculated using the FWO and KAS iso conversional kinetic approaches.[9]

Merlin Mary Mathew (2023) Industrial and household water supplies may be at risk if they contain high concentrations of dangerous metal ions or anions. Therefore, its discovery lessens the threat to ecological and human systems. In this work, we examine the biological efficacy of two carbohydrazide scaffold derivatives and the spectroscopic changes of several analytes. In order to detect Cu2+ and F in an aqueous media, we created two chemosensors, TCH and BTTCH, that rely on photoluminescence spectroscopy (PL). The AcO has also been discovered by the BTTCH with great sensitivity. Variations in the concentration's spectral maximum and color can be used as indications of the interaction that caused them. All of the complexes were found to be within the lower limits of quantification, with the exception of the complex 3TCH + F, which exhibited a substantially lower value of 8.23×10^{-8} M. According to the Benesi-Hildebrand equation, which is used to compute binding constants, the

association constant for 3TCH + F was found to be the greatest ($K = 9.39 \times 10^{-7} M^{-1}$) .The possibility of employing the chemosensors with everyday things like mouthwash and vinegar was also explored.[10]

3. MATERIALS AND METHOD

Open capillary melting points were measured using a Laboratory Devices mel-temp II equipment and have not been adjusted for temperature. [11]No additional purification of the compounds was done because they were all of analytical reagent grade. The preparation of 5-bromonitrothiophene-2-carboxylic acid has been documented. The Elementary analyse system GmbH Vario EL was used for the elemental analysis. A Nicolet Magna-IR 760 Fourier transform spectrometer with a diamond-ATR unit (ATR = attenuated total reflection) was used to acquire the infrared spectra. At 25 degrees Celsius, a Bruker Avance DPX 200 MHz NMR spectrometer captured ^{1}H (200 MHz) and ^{13}C NMR (75 MHz) spectra, calibrated against the signals of the remaining protonated solvent ([D_6]DMSO: = 2.52 (^{1}H) and 39.5 (^{13}C) ppm). Deoxygenation was performed on the NMR grade solvent [D_6]DMSO before use. Thin-layer chromatography (TLC) was performed using a solvent solution consisting of chloroform and methanol (95:5, v/v) to test the purity of the produced compounds.

Preparation of 1,3-dicyclohexyl-1-(thiophene-2-carbonyl)urea and its derivatives: a general protocol 4a and 4b

Over the course of 20 minutes, DCCI (2.81 g, 10.0 mmol) was added to a solution of 2-thiophencarboxylic acid derivatives 1 (10.0 mmol) in CH_2Cl_2 (40 mL) while stirring. The reaction mixture was then refluxed for 24 hours (TLC was used to monitor the reaction's progress). The residue was washed with 1 mol L1 Na_2CO_3 solution (2 × 20 mL) (to remove the unreacted thiophen carboxylic acid derivatives), saturated NaCl solution (2× 20 mL), and water (2× 20 mL) before being dissolved in ethyl acetate (100 mL). After that, $MgSO_4$ was used to dehydrate the organic layer. Crystals of urea derivatives 4a and 4b were obtained by evaporating the solvent under decreased pressure and then recrystallizing the isolated solid from hot ethanol.

General Procedures for the Preparation of 2-thiophenecarboxylic acid hydrazides. Methods A

Derivatives 1, 2, and 3 of 2-thiophenecarboxylic acid At room temperature, CH_3CN (80 mL) was used to dissolve or suspend the 2-thiophenecarboxylic acid derivatives 1 (40 mmol). DCCI (9.94 g, 48 mmol) and HOBt (6.48 g, 48 mmol) were each added in separate increments. For as long as it took for all of the acid to be converted to the active ester/amide combination, the mixture was agitated at r. t. and the reaction progress was monitored by TLC. The resultant liquid was cooled to 0 degrees Celsius and then gently added to a CH_3CN (40 mL) solution of hydrazine monohydrate (3.87 mL, 80 mmol). Complete addition was followed by 1 hour of stirring at 0 degrees Celsius, followed by 1 hour at 5 degrees Celsius, and then 3 hours at room temperature. Dicyclohexylurea (DCU) precipitated out, so we filtered it out and let the filtrate sit at 0 degrees Celsius for the night. The remaining DCU was filtered once more. After diluting the filtrate with water (40 mL), we extracted the CH_3CN from the water. Before drying over anhydrous Na_2SO_4, the organic layer was washed with saturated NaCl solution (2 ×25 mL), then with 5% $NaHCO_3$ in 3% NaCl solution (2 ×25 mL) to remove HOBt. The hydrazides 5a and 5b were produced via solvent removal at low pressure. The products crystallized after the crude material was dissolved in a hot ethanol solution, filtered, and cooled slowly to room temperature before being evaporated.

Plan B:

Derivatives 4a and 4b of N,N'-acyl urea Hydrazine monohydrate (0.58 mL, 12 mmol) in CH_3CN (5 mL) was added dropwise at 0 - 5 C to a solution of the appropriate urea derivative 4a or 4b (10 mmol) in CH_3CN (50 mL). The reaction mixture's temperature was then increased slowly to room temperature, where it remained for roughly 6 hours while being stirred. Filtration was used to get rid of the precipitated dicyclohexylurea (DCU), and then the filtrate was stored at 0 degrees Celsius for an additional night before being filtered again. The residue was dissolved in ethyl acetate (150 mL) after CH_3CN had been evaporated at low pressure. The organic layer was washed with saturated aqueous Na_2CO_3 (3.25 w/w) and water (3.25 v) before being dried over anhydrous $MgSO_4$, evaporated, and recrystallized from ethanol to get a crude product 5.

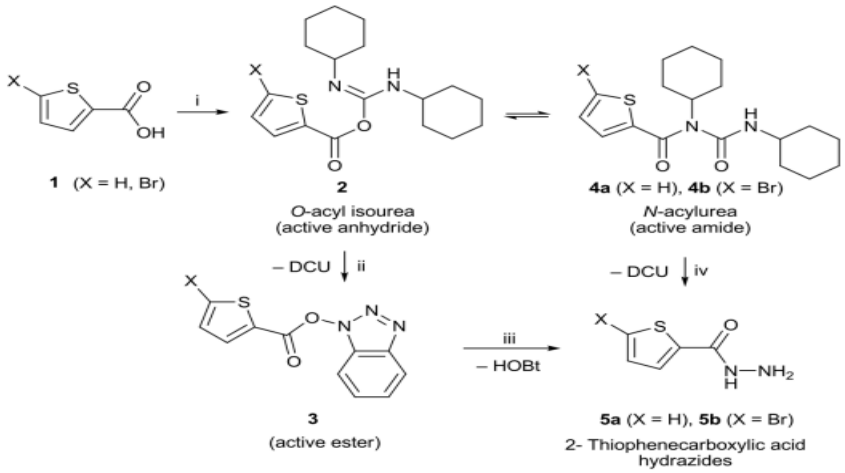
Preparation of 1,3-dicyclohexyl-1-(heteroaryl/aryl/aralkyl-2-carbonyl)urea derivatives generally follows these steps: 6a - g

After recrystallization from the proper solvent, the N-acyl urea derivatives 6a-g were obtained from the heteroaryl/aryl/aralkyl carboxylic acids used in the preparation of 4a and 4b.

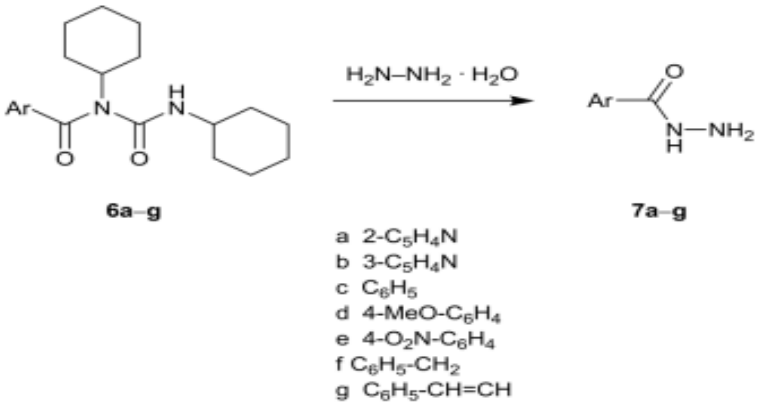
The 7a-g Substituted Carboxyhydrazides: Preparation by General Methods

The corresponding carboxylic acids were used in the synthesis of 5a and 5b, where the carboxyl group was activated with HOBt/DCCI following method A, or in the synthesis of N-acyl urea derivatives 6a-g following method B, the same procedure described for the synthesis of thiophene carbohydrazides. The IR, and ^{1}H NMR data of the discovered hydrazides provided insight into their structures.

4.RESULTS



Scheme 1. Synthesis of substituted hydrazides.



Scheme 2. Synthesis of substituted hydrazides.

Table 1. Physical and spectral data for 6a – g.

Ar (Formula)	Yield	M. p. (◦C) exp. /lit sol. crystal	IR cm^{-1}	^{1}H NMR (200 MHz)
2-C_5H_4N- ($C_{19}H_{27}N_3O_2$)	32	142.4 / 144.5 EtOH	3300, 3020, 2930, 1691, 1645	($CDCl_3$): δ = 0.8 – 1.99 (m, 20H, Cy CH_2), 3.34 – 3.42 (m, 1H,Cy CH), 3.98 – 4.18 (m, 1H, Cy CH), 6.02 (br d, J = 8.2, 1H, NH), 7.55 – 8.57 (m, 4H, Py H)
3-C_5H_4N- ($C_{19}H_{27}N_3O_2$)	48	170.2 / 171.5 EtOH	3323, 3005, 2968, 1675, 1652	($CDCl_3$):δ = 1.1 – 1.79 (m, 20H, Cy CH_2), 3.54 – 3.67 (m, 1H,Cy CH), 4.44 – 4.54 (m, 1H, Cy CH), 6.10 (br d, J = 7.9, 1H,NH), 7.50 – 8.76 (m, 4H, Py H)
C_6H_5 - ($C_{20}H_{28}N_2O_2$)	73	163.5 / 162.7 $CHCl_3$	3278, 3042, 2933, 1706, 1639	($CDCl_3$): δ = 0.72 – 2.18 (m, 20H, Cy CH_2) , 3.21 – 3.58 (m, 1H, Cy CH), 3.85 – 4.06 (m, 1H, Cy CH), 6.11 (br, d, J = 7.9, 1H),7.19 – 7.48 (m, 5H, Ar H)

4-MeO-C_6H_4 - ($C_{21}H_{30}N_2O_3$)	70	151.3 / 151.0 Acetone	3302, 2999, 2950, 1685, 1633	($CDCl_3$): δ = 0.90 – 2.41 (m, 20H, Cy CH_2) , 3.52 – 3.70 (m, 1H,Cy CH), 3.83 (s, 3H, OCH_3), 3.91 – 4.00 (m, 1H, Cy CH), 6.1 (br d, J = 7.8, 1H, NH), 6.80 – 7.51 (m, 4H, Ar H)
4-NO_2 -C_6H_4 - ($C_{20}H_{27}N_3O_4$)	84	202.4 / 204.0 AcOEt	3298, 3001, 2949, 1699, 1645	($CDCl_3$):δ = 0.83 – 1.95 (m, 20H, Cy CH_2), 3.40 – 3.55 (m, 1H,Cy CH), 3.98 – 4.03 (m, 1H, Cy CH), 6.12 (br d, J = 7.75, 1H, NH), 7.07 – 8.60 (m, 4H, Ar H)
C_6H_5 -CH_2 - ($C_{21}H_{30}N_2O_2$)	79	114.6 / 115.8 EtOH-Et_2O	3338, 3098, 2954, 1700, 1649	($CDCl_3$): δ = 0.96 – 2.03 (m, 20H, Cy CH_2) , 3.45 (s, 2H), 3.55 – 3.72 (m, 1H, Cy CH), 3.90 – 4.05 (m, 1H, Cy CH), 6.23 (br d, J = 8.17, 1H, NH), (m, 1H), 7.27 – 7.43 (m, 5H, Ar H)
$C_{22}H_{30}N_2O_2$	70	164.6 /165 $CHCl_3$	3320, 3000, 2938, 1708, 1650, 1607	($CDCl_3$): δ = 0.85 – 2.20 (m, 20H, Cy CH_2), 3.38 – 3.52 (m, 1H, Cy CH), 4.01 – 4.33 (m, 1H, Cy CH), 6.69 (d, J = 15.20, 1H, CH), 6.98 (br d, J = 8.20, 1H, NH), 7.27 – 7.58 (m, 5H, Ar H), 7.69 (d, J = 15.30, 1H, CH)

Table 2. Physical and spectral data for 7a – g.

Ar (Formula)	Y	M. p. (◦C) exp. /lit sol. crystal	IR cm^{-1}	^1H NMR (200 MHz)
2-C_5H_4N- ($C_6H_7N_3O$)	76	226.8 / 227.8 Et_2O	3320,3199, 3015 1669, 1635	($CDCl_3$): δ = 4.61 (s, 2H, NH_2), 7.51 (t, 1H, Py H), 7.89 (t, 1H, Py H), 8.18 (d, 1H, J = 7.4, Py H), 8.98 (d, 1H, J = 4.6, Py H), 9.63 (br. s, 1H, CONH)
3-C_5H_4N- ($C_6H_7N_3O$)	86	160.2 / 161.3 EtOH	3325,3205, 3030,1665, 1623	($CDCl_3$):δ = 4.48 (br s, 2H, NH_2), 7.56 (t, 1H, Py H),8.12 (d, 1H,J = 4.6, Py H), 8.58 (d, 1H, J = 7.4, Py H), 8.99 (s, 1H, Py H), 9.60 (br. s, 1H, CONH)
C_6H_5 – ($C_7H_8N_2O$)	79 / 90	105.7 / 108.9 AcOEt	3300,3198, 2966,1660, 1615	($CDCl_3$): δ = 4.31 (s, 2H, NH_2), 7.42 (m, 3H, Ar H), 7.78 (dd, 2H, J = 7.9, 1.7, Ar H), 8.68 (s, 1H, CONH)
4-MeO-C_6H_4 ($C_8H_{10}N_2O_2$)	68 / 83	135.7 / 128.13 EtOH	3345,3187, 3028,3028, 2837,1661, 1522	($CDCl_3$):δ = 3.85 (s, 3H, OCH3), 4.21 (s, 2H, NH_2),6.94 (d, 2H, Ar H), 7.71 (d, 2H, Ar H), 8.19 (s, 1H,CONH)
4-NO_2 -C_6H_4- ($C_7H_7N_3O_3$)	75 / 83	212.4 / 216.8 EtOH	3387,3210, 3028,1684, 1525	($CDCl_3$):δ = 4.63 (s, 2H, NH_2), 7.89 (d, 2H, Ar H),8.09 (d, 2H, Ar H), 8.60 (s, 1H, CONH)
C_6H_5 -CH_2 - ($C_8H_{10}N_2O$)	68 / 80	113/5 / 113.5 EtOH	3306,3098, 1660,1643, 1534	($CDCl_3$):δ = 3.48 (s, 2H, CH2), 4.22 (br s, 2H, NH_2),6.97 – 7.26 (m, 5H, phenyl), 8.68 (s, 1H, CONH)
C_6H_5 -CH=CH- ($C_9H_{10}N_2O$)	82 / 85	116.7 / 116.7 C_6H_6	3316,3215, 1651,1621, 1561	($CDCl_3$):δ = 4.03 (br s, 2H, NH_2), 6.40 (d, J= 15.6,1H), 7.31 – 7.37 (m, 3H, Ar H), 7.48 – 7.51 (m, 2H, ArH), 7.68 (d, J= 15.6, 1H), 8.81 (s, 1H, CONH)

5.DISCUSSIONS

The 2-thiophenecarboxylic acid hydrazide and 5-bromo-2-thiophenecarboxylic acid hydrazide targets were synthesized in three simple processes utilizing low-cost, readily-available ingredients. In the first stage, 2-thiophenecarboxylic acid derivatives were added to DCCI, forming the unstable N,N-dicyclohexylcarbamidic thiophene-2-carboxylic anhydride (2, O-acyl isourea). [13]Compound 2 can be activated with hydroxy benzotriazole (HOBt) to get 1-H-benzo[d][1,2,3]triazol-1-yl thiophene-2-carboxylate (3, activated or active ester), or it can rearrange to generate 1,3-dicyclohexyl-1-(thiophene-2-carbonyl)urea. According to Scheme 1, the appropriate hydrazides were obtained by further hydrazinolysis of N-acyl urea 4 or the active ester 3. Treatment of N-acyl urea with aryl, heteroaryl, and substituted aryl radicals yielded the hydrazines 7a-g (Scheme 2). Substitution of hydrazides in a synthesis. combination of aralkyl 6a-g with hydrazine hydrate. [15]

6.CONCLUSIONS

Under moderate circumstances, 2-thiophenecarboxylic acids and their heterocyclic aryl or aralkyl analogues can be converted to their corresponding hydrazides by hydrazinolysis of the intermediate N-acyldicyclohexyurea derivatives in good to outstanding yields.

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