2-Thiophenecarbohydrazides: A Novel Efficient Method for the Synthesis of 2-Thiophenecarbohydrazide

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Hydrazinolysis of carboxylic acid esters in alcoholic solutions is the standard method for preparing carbohydrazides (carboxylic hydrazides). Here we report an efficient process, involving the reaction of activated esters or amides with hydrazine, for the preparation of thiophenecarbohydrazides in yields larger than 90 % and high purity. With this new method, a series of heteroaryl-, aryl-, or aralkyl-substituted carbohydrazides were synthesized and characterized. The X-ray crystal structure of 2-thiophenecarbohydrazide (thiophene-2-carboxylic hydrazide, 2-thenoyl-hydrazine) has revealed that it crystallizes in the monoclinic system, space group $P2_1/c$, with cell parameters of $a = 6.1202(2)$, $b = 8.3907(3)$, $c = 12.5332(5)$ Å, $\beta = 98.6577(11)^\circ$, $Z = 4$, $R(F) = 0.0455$ and $wR(F^2) = 0.1805$, $T =$ 293 K.

Key words: Carbohydrazides, Thiophenecarbohydrazide, 2-Thiophenecarboxylic Hydrazide, 2-Thenoyl-hydrazine, Hydrogen Bonding

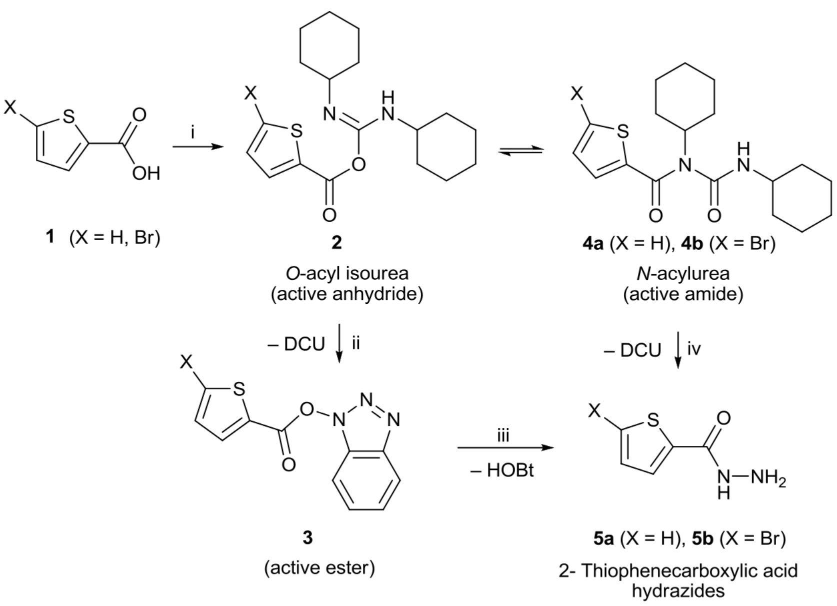
Introduction

In the synthesis of organic and natural products, it is often required to introduce a carbohydrazide group into molecules. Hydrazides have received special interest due to their potential applications as building blocks in the syntheses of, *e. g.*, hydrazones, Schiff bases, and coordination compounds [1].

To date, a variety of procedures have been developed to prepare carbohydrazides. A basic method involves the preparation of acyl anhydrides and acid chlorides which subsequently react rapidly with hydrazine to give the corresponding carbohydrazides [2]. However, acid chlorides and anhydrides are so reactive that it is difficult to stop the reaction at the end of the monoacylation step. The standard method to prepare carbohydrazides is the hydrazinolysis of the corresponding esters [3] which has a requirement of preparing esters from corresponding acids. Esters seldom produce significant amounts of diacylhydrazine, but less reactive esters may require inconveniently longer reaction times and/or harsh reaction conditions. The use of inclusion complexes of hydroquinone and hydrazine in solid-state hydrazinolysis of esters has also been reported [4]. Other alternative methods for the direct preparation of carbohydrazides from acids are inefficient, and few examples have been reported for this synthesis under microwave irradiation or *via* activated esters formed by catalytic coupling reagents [5 – 7]. So the development of a facile and efficient method to prepare carbohydrazides from their corresponding carboxylic acids is a valuable task.

Among the hydrazides, 2-thenohydrazides have attracted considerable attention due to the biological activity of the 2-thiophene moiety which has been widely recognized and practically applied in several drugs [8 – 10], herbicides [11] and fungicides [12, 13]. Thiophenecarboxylic hydrazides were tested for antituberculous activity [14] and found to show β-adrenergic blocking activities [15]. Furthermore, 2-thiophenecarboxylic hydrazide (2-thiophenecarbohydrazide, 2-thenoyl-hydrazine) is a known ligand in transition metal complexes. The compound coordinates with the carbonyl oxygen atom and the NH_2 nitrogen atom forming five-membered metal-chelate rings with manganese, cobalt, nickel, copper [16], zinc [16, 17], cadmium [16, 18], palladium [19], and ruthenium [20].

Therefore, we considered to investigate the reactivity of carbodiimides with ester and/or amide functionality towards hydrazinolysis. We describe herein

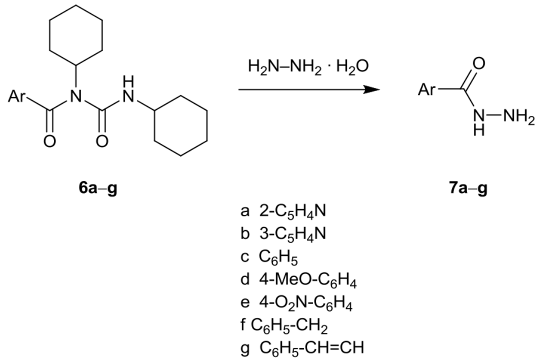


Scheme 1. i) Catalytic DCCI (dicyclohexylcarbodiimide), acetonitrile (CH_3CN), 0 °C, 5 °C, r. t.; ii) HOBt, 0 °C; iii) hydrazine hydrate ($N_2H_4 \cdot H_2O$), CH_3CN, 0 °C, 5 °C, r. t.; iv) $N_2H_4 \cdot H_2O$, CH_3CN, 0–5 °C, r. t.; DCU = dicyclohexylurea, HOBt = hydroxybenzotriazole.

an efficient procedure for the direct conversion of 2-thiophenecarboxylic acid derivatives into hydrazides in excellent yields under mild conditions through i) the preparation of activated 2-thiophencarboxylate esters and/or amides using 1-hydroxybenzotriazole (HOBt) and dicyclohexylcarbodiimide (DCCI) and ii) the treatment of these activated esters or mixed anhydrides with hydrazine. Also, the crystal structure of 2-thiophenecarbohydrazide is reported.

Results and Discussion

Synthesis of the target compounds 2-thiophenecarboxylic acid hydrazide and 5-bromo-2-thiophenecarboxylic acid hydrazide (**5**) was achieved in three steps using inexpensive commercially available materials. The first step involved formation of unstable *N*,*N*′-dicyclohexylcarbamidic thiophene-2-carboxylic anhydride (**2**, *O*-acyl isourea) through addition of 2-thiophenecarboxylic acid derivatives (**1**) to DCCI. Compound **2** may undergo rearrangement forming 1,3-dicyclohexyl-1-(thiophene-2-carbonyl)urea (**4**, *N*-acylurea) or become activated with hydroxybenzotriazole (HOBt) to give 1-*H*-benzo[*d*][1,2,3]triazol-1-yl thiophene-2-carboxylate (**3**, activated or active ester). Subsequent hydrazinolysis of *N*-acylurea **4** or the active ester **3** afforded the corresponding hydrazides according to Scheme 1.



Scheme 2. Synthesis of substituted hydrazides.

Hydrazides **7a–g** were also synthesized by treating *N*-acylurea with aryl, heteroaryl, substituted aryl and aralkyl groups **6a–g** with hydrazine hydrate (Scheme 2).

The molecular structure of 2-thiophenecarboxylic hydrazide **5a** has been determined (Fig. 1). The molecule is rather planar with torsion angles of the *cis*-oriented atoms being less than 10°.

The packing is controlled by N–H···N and N–H···O hydrogen bonding (Fig. 2) including pairs of molecules related by a center of symmetry with N1–H2···N2 hydrogen bonds in $R_2^2(6)$ rings (Fig. 2) and a C(4) chain graph-set motif along ···O=C–N1–N2–H···O [21].

Conclusion

An efficient one-pot conversion of 2-thiophenecarboxylic acids and heterocyclic aryl, or aralkyl analogs

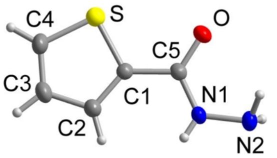


Fig. 1 (color online). Molecular structure of 2-thiophenecarboxylic hydrazide **5a**. Selected bond lengths (Å) and angles (deg): S–C4 1.7134(15), S–C1 1.7234(13), O–C5 1.2362(16), N1–C5 1.3337(18), N1–N2 1.4203(16); C4–S–C1 91.58(7), C5–N1–N2 121.72(11), O–C5–N1 122.52(13), O–C5–C1 122.04(12); torsion angles (deg): N2–N1–C5–O 9.5(2), S–C1–C5–O 4.30(18).

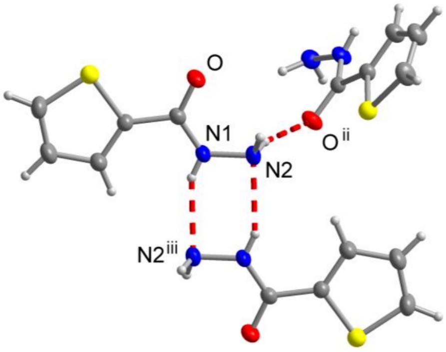


Fig. 2 (color online). Hydrogen bonding motif in the crystal structure of **5a**. Distances (Å) and angles (deg): N1–H 0.762(18), H$\cdots$N2^{iii} 2.223(18), N1$\cdots$N2^{iii} 2.9229(17); N1–H$\cdots$N2^{iii} 153.1(17); N2–H 0.841(19), H$\cdots$O^{ii} 2.139(19), N2$\cdots$O^{ii} 2.9530(16); N2–H$\cdots$O^{ii} 162.7(17). Symmetry transformations: ii = $-x+2, y+1/2, -z+1/2$; iii = $-x+2, -y+1, -z$.

into the corresponding hydrazides in good to excellent yields under mild conditions involves hydrazinolysis of the intermediate *N*-acyldicyclohexyurea derivatives. In the crystal structure of (2-thenoyl) hydrazine, molecules are associated into a 3D framework by a combination of N–H$\cdots$N and three-center N–H$\cdots$O hydrogen bonds.

Experimental Section

Melting points were determined in open capillaries with a Laboratory Devices mel-temp II apparatus and are uncorrected. All chemicals were of analytical reagent grade and were used without further purification. 2-thiophenecarboxylic acid was obtained from ABCR, 1-hydroxybenzotriazole (HOBt) and dicyclohexylcarbodiimide (DCCI) from Sigma, and hydrazine hydrate from Fluka. 5-Bromonitrothiophene-2-carboxylic acid was prepared by a reported method [22]. Elemental analyses were carried out on a Vario EL instrument from Elementaranalysensysteme GmbH. IR spectra were recorded on a Nicolet Magna-IR 760 Fourier-transform spectrometer equipped with a diamond-ATR unit (ATR = attenuated total reflection). The ^{1}H (200 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance DPX 200 MHz NMR spectrometer at 25 °C with calibration against the signals of the residual protonated solvent ([D$_6$]DMSO: δ = 2.52 (^{1}H) and 39.5 (^{13}C) ppm). The NMR-grade solvent [D$_6$]DMSO was deoxygenated prior to use. High-resolution mass spectra were taken as EI- and CI-MS using a Thermo-Finnigan TSQ 700 Mass spectrometer at 70 eV, with NH$_3$ as ionization gas for CI (chemical ionization). Peaks reported are for the major isotopes ^{12}C and ^{79}Br. The purities of the synthesized compounds were checked by thin-layer chromatography (TLC) conducted on Merck silica using the solvent system chloroform-methanol (95 : 5, v : v).

*General procedures for the preparation of 1,3-dicyclohexyl-1-(thiophene-2-carbonyl)urea derivatives **4a** and **4b***

To a solution of 2-thiophencarboxylic acid derivatives **1** (10.0 mmol) in CH$_2$Cl$_2$ (40 mL), was added DCCI (2.81 g, 10.0 mmol) in portions with stirring over a period of 20 min. Then the reaction mixture was refluxed for 24 h (reaction progress was checked by TLC). After the removal of the solvent under reduced pressure, the residue was dissolved in ethyl acetate (100 mL), filtered and washed with 1 mol L^{-1} Na$_2$CO$_3$ solution (2 × 20 mL) (to remove the unreacted thiophenecarboxylic acid derivatives), with saturated NaCl solution and finally with water (2 × 20 mL). Then the organic layer was dried over MgSO$_4$. The solvent was evaporated under reduced pressure, and the isolated solid was recrystallized from hot ethanol to yield crystals of urea derivatives **4a** and **4b**.

*1,3-Dicyclohexyl-1-(thiophene-2-carbonyl)urea (**4a**)*: yield 3.06 g (91.7 %). M. p. 101 – 103 °C (lit.: 105 °C [23]).

*1,3-Dicyclohexyl-1-(5-bromothiophene-2-carbonyl)urea (**4b**):* pale-yellow crystals (yield 3.59 g, 87.0 %). – M. p. 119 – 121 °C. – IR (ATR): ν = 3285 (m, br, N-H, H-bonded), 2956 (w, sh, C-H-cyclohexyl), 3075 (m, sh, C-H, aromatic), 1708.5 (s, sh, C=O, urea), 1666 (s, sh, C=O, amide), 1541, 1516, 1420, 1358 (m, sh, CSC thiophene), 1229, 908, 810, 743, 599, 567 cm^{-1}. – ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 7.61 (d, *J* = 4.0 Hz, 1 H, 3-Ar-H), 7.08 (d, *J* = 3.9 Hz, 1 H, 4-Ar-H), 6.38 (d, *J* = 9.2 Hz, 1 H, NH), 4.12 – 3.83 (m, 1 H, C*H*-N(CO)$_2$), 3.66 – 3.54 (m, 1H, C*H*-NHCO), 0.86 – 1.72 (m, 20H, all CH$_2$-cyclohexyl). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 161.7 (amide C=O), 153.9 (urea C=O), 137.9 (aromatic C), 135.2 (aromatic CH), 130.4 (aromatic CH), 120.3 (aromatic C-Br), 57.3 (cyclohexyl-*C*H-N), 51.5 (cyclohexyl-*C*H-NH), 32.3, 30.2, 25.6, 24.9, 24.3 and 23.9 (cyclohexyl-CH$_2$). – MS (EI, 70 eV): m/z (%) = 412 (89) [M]$^+$, 316 (46) [M–C$_6$H$_{11}$N]$^+$, 190 (100) [C$_5$H$_2$BrOS]$^+$. – MS (CI(NH$_3$)): m/z(%) = 430 (23) [M+NH$_4$]$^+$, 412 (100) [M]$^+$. – Anal. for

Table 1. Physical and spectral data for 1,3-dicyclohexyl-1-(heteroaryl/aryl/aralkyl-2-carbonyl)urea derivatives **6a – g**.

Nr.	Ar (Formula)	M. p. (°C) exp. / lit. solv. of cryst.	Y (%)	EA (%) calcd./ found C	H	N	IR (cm^{-1})	^1H NMR (200 MHz)	Ref.
a	2-C_5H_4N- ($C_{19}H_{27}N_3O_2$)	142 – 4 / 144 – 5 EtOH	32	69.27 68.98	8.26 8.02	12.76 13.00	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)	[30]
b	3-C_5H_4N- ($C_{19}H_{27}N_3O_2$)	170 – 2 / 171.5 EtOH	48	69.27 69.42	8.26 8.13	12.76 12.78	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)	[31]
c	C_6H_5- $C_{20}H_{28}N_2O_2$	163 – 5 / 162 – 7 $CHCl_3$	73	73.14 73.00	8.59 8.71	8.53 8.50	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)	[32]
d	4-MeO-C_6H_4- $C_{21}H_{30}N_2O_3$	151 – 3 / 151 Acetone	70	70.36 69.99	8.44 8.68	7.81 7.92	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)	[33]
e	4-NO_2-C_6H_4- $C_{20}H_{27}N_3O_4$	202 – 4 / 204 AcOEt	84	64.32 64.30	7.29 7.41	11.25 11.32	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)	[34]
f	C_6H_5-CH_2- $C_{21}H_{30}N_2O_2$	114 – 6 / 115 – 8 EtOH-Et_2O	79	73.65 73.55	8.83 8.80	8.18 8.21	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)	[35]
g	C_6H_5-CH=CH- $C_{22}H_{30}N_2O_2$	164 – 6 /165 $CHCl_3$	70	74.54 74.52	8.53 8.48	7.90 7.85	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)	[32]

$C_{18}H_{25}BrN_2O_2S$ (412.37): calcd. C 52.30, H 6.10, N 6.78, S 7.76; found C 52.15, H 6.22, N 6.91, S 7.34.

*General procedures for the preparation of 2-thiophenecarboxylic acid hydrazides **5a** and **5b***

*Method A: From 2-thiophenecarboxylic acid derivatives **1** through **2** and **3***

The 2-thiophenecarboxylic acid derivatives **1** (40.0 mmol) were dissolved or suspended in CH_3CN (80 mL) at r. t. DCCI (9.94 g, 48 mmol) was added in one portion followed by HOBt (6.48 g, 48 mmol). The mixture was stirred at r. t., and the reaction progress was monitored by TLC until all of the acid was converted to the activated ester/amide mixture. A solution of hydrazine monohydrate (3.87 mL, 80 mmol) in CH_3CN (40 mL) was then slowly added to the resulting mixture while the temperature was maintained at 0 °C. After complete addition, the reaction mixture was stirred at 0 °C for another 1 h, at 5 °C for 1 h and finally at room temperature for 3 h. The precipitated dicyclohexylurea (DCU) was removed by filtration and the filtrate allowed to stand at 0 °C overnight. Then it was filtered again from the residual DCU. The filtrate was then diluted with water (40 mL), and the aqueous CH_3CN mixture was extracted with EtOAc. 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, and finally dried over anhydrous Na_2SO_4. Removal of the solvents under reduced pressure yielded the hydrazides **5a** and **5b**. The products were crystallized by dissolving the crude material in hot ethanol solution, filtering and slow cooling to r. t. with subsequent evaporation.

*2-Thiophenecarboxylic acid hydrazide (**5a**):* yield 4.94 g (87 %) (lit.: hydrazinolysis of the corresponding esters: 80 % [24]). Colorless solid. – M. p. 138 °C (lit.: 136–139 °C [24]).

*5-Bromo-2-thiophenecarboxylic acid hydrazide (**5b**)***:** yield 8.22 g (93 %) (lit.: hydrazinolysis of the corresponding esters: 85% [24]). Colorless solid. – M. p. 146 °C (lit.: 144 °C [24]).

*Method B: From N,N'-acylurea derivatives **4a** and **4b***

To a solution of the appropriate urea derivatives **4a** or **4b** (10 mmol) in CH_3CN (50 mL), a solution of hydrazine monohydrate (0.58 mL, 12 mmol) in CH_3CN (5 mL) was added dropwise at 0–5 °C. Then, the temperature of the reaction mixture was gradually raised to r. t., and the mixture was stirred at this temperature for about 6 h. The precipitated dicyclohexylurea (DCU) was removed by filtration, the filtrate was kept at 0 °C overnight and re-filtered to remove residual DCU. After CH_3CN had been evaporated under reduced pressure, the residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with saturated

Table 2. Physical and spectral data for carboxylic acid hydrazides **7a**–**g**.

Nr.	Ar (Formula)	M. p. (°C) exp. / lit. solv. of cryst.	Y classic/DCC	EA (%) calcd./ found C	H	N	IR (cm^{-1})	^1H NMR (200 MHz)	Ref.
a	2-C_5H_4N- ($C_6H_7N_3O$)	226–8 / 227–8 Et_2O	76 / 84	52.55 52.50	5.14 5.19	30.64 30.85	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)	[36]
b	3-C_5H_4N- ($C_6H_7N_3O$)	160–2 / 161–3 EtOH	86 / 95	52.55 52.34	5.14 5.25	30.64 30.56	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)	[37]
c	C_6H_5-($C_7H_8N_2O$)	105–7 / 108–9 AcOEt	79 / 90	61.75 61.76	5.92 6.11	20.58 20.48	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)	[36]
d	4-MeO-C_6H_4- ($C_8H_{10}N_2O_2$)	135–7 / 128–130 EtOH	68 / 83	57.95 57.82	6.07 6.18	16.86 16.70	3345, 3187, 3028, 3028, 2837, 1661, 1522	($CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 4.21 (s, 2H, NH_2), 6.94 (d, 2H, Ar H), 7.71 (d, 2H, Ar H), 8.19 (s, 1H, CONH)	[38]
e	4-NO_2-C_6H_4- ($C_7H_7N_3O_3$)	212–4 / 216–8 EtOH	75 / 83	46.41 46.40	3.89 3.81	23.20 23.19	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)	[38]
f	C_6H_5-CH_2- ($C_8H_{10}N_2O$)	113–5 / 113–5 EtOH	68 / 80	63.98 64.00	6.71 6.56	18.65 18.72	3306, 3098, 1660, 1643, 1534	($CDCl_3$): δ = 3.48 (s, 2H, CH_2), 4.22 (br s, 2H, NH_2), 6.97–7.26 (m, 5H, phenyl), 8.68 (s, 1H, CONH)	[37]
g	C_6H_5-CH=CH- ($C_9H_{10}N_2O$)	116–7 / 116–7 C_6H_6	82 / 85	66.65 66.90	6.21 6.00	17.27 17.18	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, Ar H), 7.68 (d, J= 15.6, 1H), 8.81 (s, 1H, CONH)	[39]

aqueous Na_2CO_3 (3 × 25 mL) and water (3 × 25 mL), dried over anhydrous $MgSO_4$, and evaporated to give a crude product **5**, which was recrystallized from ethanol.

*2-Thiophenecarboxylic acid hydrazide (**5a**):* yield 4.94 g (87 %) (lit.: hydrazinolysis of the corresponding esters: 80 % [23]). Colorless solid. – M. p. 138 °C (lit.: 136–139 °C [23]). – ^1H NMR (200 MHz, $[D_6]DMSO$, 25 °C, TMS): δ = 4.40 (br, s, 2H, NH_2), 7.01 (dd, J = 3.5 Hz, 1H, 4-Th-H), 7.52 (d, J = 2.8 Hz, 1H, 3-Th-H), 7.83 (d, J = 4.7 Hz, 1H, 5-Th-H), 8.45 (br, s, 1H, CONH). – MS ($CI(NH_3)$): m/z (%) = 160 (9) $[M+NH_4]^+$, 143 (100) $[M+H]^+$, 111 (14) $[(C_4H_3S)CO]^+$. – Anal. for $C_5H_6N_2OS$ (142.18): calcd. C 42.24, H 4.25, N 19.70, S 22.55; found C 42.41, H 4.28, N 20.00, S 22.65.

*5-Bromo-2-thiophenecarboxylic acid hydrazide (**5b**):* yield 8.22 g (93 %) (lit.: hydrazinolysis of the corresponding esters: 85 % [24]). Colorless solid. – M. p. 146 °C (lit.: 144 °C [24]). – ^1H NMR (200 MHz, $[D_6]DMSO$, 25 °C, TMS): δ = 4.45 (br, s, 2H, NH_2), 7.35 (d, 1H, J = 4.0 Hz, 4-Th-H), 7.37 (d, 1H, J = 4.0 Hz, 3-Th-H), 9.07 (br, s, 1H, CONH). – MS (EI, 70 eV): m/z (%) = 221 (35) $[M]^+$, 190 (100) $[(5\text{-}Br\text{-}C_4H_2S)CO]^+$. – Anal. for $C_5H_5BrN_2OS$ (221.07): calcd. C 27.16, H 2.28, N 12.67, S 14.50; found C 27.38, H 2.21, N 12.41, S 14.65.

*General procedures for the preparation of 1,3-dicyclohexyl-1-(heteroaryl/aryl/aralkyl-2-carbonyl)urea derivatives **6a–g***

N-Acylurea derivatives **6a–g** were prepared from the heteroaryl/aryl/aralkyl carboxylic acids as described for **4a** and **4b** and recrystallized from an appropriate solvent as shown in Table 1.

*General procedures for preparation of substituted carbohydrazides **7a–g***

These compounds were obtained from the corresponding carboxylic acids either *via* the activation of the carboxyl group with HOBt/DCCI according to method A in the synthesis of **5a** and **5b** or by conversion into *N*-acylurea derivatives **6a–g** followed by hydrayzinolysis using the same procedure (method B) as described for the synthesis of thiophenecarbohydrazides. The obtained hydrazides were characterized by their EA, IR and ^1H NMR data (Table 2).

X-Ray structure determination

A crystal of 2-thiophenecarbohydrazide was selected under a polarizing microscope. *Data collection*: Rigaku R-axis Spider Image plate detector diffractometer, MoK_α radiation (λ = 0.71073 Å), graphite monochromator, r. t., double-pass method ω scan; data collection, cell refinement and data reduction with CRYSTALCLEAR [25], empirical (multi-scan) absorption correction with ABSCOR [26]. *Structural Analysis and Refinement*: The structure was solved by Direct Methods (SHELXS [27]), refinement was carried out by full-matrix least-squares on F^2 using SHELXL [27]; all non-hydrogen positions were refined with anisotropic temperature factors; hydrogen atoms for aromatic CH groups were positioned geometrically (C–H = 0.93 Å) and refined using a riding model, with $U_{iso}(H)$ = 1.2 $U_{eq}(C)$; H atoms at the nitrogen atoms were found and refined with $U_{iso}(H)$ = 1.2 $U_{eq}(N)$. Graphics were drawn with DIAMOND [28]. Computations on the supramolecular interactions were carried out with PLATON for Windows [29]. Crystal data and details on the structure refinements are given in Table 3.

Table 3. Crystal structure data for **5a**.

Formula	$C_5H_6N_2OS$
M_r	142.18
Crystal size, mm^3	0.58 × 0.47 × 0.28
Crystal system	monoclinic
Space group	$P2_1/c$
a, Å	6.1202(2)
b, Å	8.3907(3)
c, Å	12.5332(5)
β, deg	98.6577(11)
V, Å^3	636.28(4)
Z	4
D_{calcd}, g cm^{-3}	1.48
$\mu(MoK_\alpha)$, cm^{-1}	0.4
$F(000)$, e	296
hkl range	+6, ±10, ±16
$((\sin\theta/\lambda)_{max}$, Å^{-1}	0.648
Refl. measd. / unique / R_{int}	11734 / 1442 / 0.0273
Param. refined	91
$R(F)$ / $wR(F^2)^{a,b}$ (all refl.)	0.0347 / 0.0769
GoF $(F^2)^c$	1.074
$\Delta\rho_{fin}$ (max / min), e Å^{-3}	0.276 / −0.168

[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; [b] $wR = [\Sigma w(F_o{}^2 - F_c{}^2)^2/\Sigma w(F_o{}^2)^2]^{1/2}$, $w = [\sigma^2(F_o{}^2) + (AP)^2 + BP]^{-1}$, where $P = (\mathrm{Max}(F_o{}^2, 0) + 2F_c{}^2)/3$; [c] $\mathrm{GoF} = [\Sigma w(F_o{}^2 - F_c{}^2)^2/(n_{obs} - n_{param})]^{1/2}$.

CCDC 851335 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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