Parallel Synthesis of a Library of Acylsemicarbazides Using a Solution-Phase One-Pot Method and Their Evaluation as Crop-Protection Agents

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Abstract: A solution-phase one-pot synthesis of a 40-member acylsemicarbazide library is outlined. The acylsemicarbazides were prepared by reacting various hydrazides with N,N’-carbonyldiimidazole (CDI) to generate 1,3,4-oxadiazole-2-one intermediates, which were then opened in situ with amines. Purification of the majority of cases was accomplished through filtration of the precipitated product in generally good yields and with ≥ 95% purities. An analogous synthesis of acylthiosemicarbazides was accomplished using N,N’-thiocarbonyldiimidazole (TCDI). The library was then assayed for herbicidal, insecticidal, fungicidal and plant growth regulatory behavior.

Key words: acylsemicarbazides, acylthiosemicarbazides, 1,3,4-oxadiazol-2-one, solution phase, library, crop protection

There are numerous small molecules containing the semicarbazide moiety, which have been shown to possess interesting biological activity. They have been used as peptidomimetics,1 and also as anti-convulsant analogues of functionalized amino acids.2 In the area of crop protection there has been considerable interest in semicarbazides. Wing demonstrated that N-tert-butyl-N,N’-dibenzoylhydrazine was a novel type of insect growth regulator, acting as an ecdysone agonist, leading to premature molting.3 Subsequently, N-tert-butyl-N,N’-diacylhydrazines have been extensively studied and proved to be an important, environmentally safe and selective type of insecticide active against lepidopterous pests.4 The semicarbazide analogues were also found to show good larvicidal activity, as well as potential anticancer activities.5 We now report the development of a one-pot procedure for the parallel synthesis of a library of acylsemicarbazides, which have been tested against a broad panel of assays for crop protection behavior.

In recent years, combinatorial chemistry has played a greater role in drug discovery and optimization, and a considerable body of work now exists for both solid-phase organic synthesis (SPOS),6 liquid-phase organic synthesis (LPOS),7 as well as solution-phase organic synthesis.8 Solution-phase organic synthesis is often the method of choice for the synthesis of small to medium sized libraries of small non-peptidic molecules, since it avoids the well-known developmental problems necessary for establishing robust and reproducible chemistry using polymer-supported methods. Solution-phase organic synthesis is also readily amenable to the synthesis of large amounts of material. However, purification of libraries generated using solution-phase parallel synthesis can be very challenging. There are several strategies that have been developed to solve this problem, including the use of automated semi-preparative HPLC, liquid–liquid extraction,9 fluorous phase,10 or polymer supported reagents or scavengers.11 Perhaps the most simple strategy, when applicable, is library purification by direct precipitation of the insoluble products or by addition of an appropriate solvent to induce precipitation.12 For example, heterocycles such as pyridinethiones, pyridinones and thiopyridinones, can be directly precipitated.12a Other heterocycles have been precipitated as HCl salts, such as isoxazolines and isoxazoles,12b substituted pyrrolidines,12c and dihydrophenyl triazines.12d Non-cyclic Passerini reaction products have also been isolated via filtration by Pirrung.12e The use of chemical tags to induce precipitation has also been examined, neatly overcoming the requirement that the products must exist as solids.13,14 Wilcox has used chemical tags called precipitons that allow for precipitation of the product from solution once the reaction is complete.13 Purification by precipitation is also employed in LPOS, where reactions are carried out on a soluble polymer support such as poly(ethyleneglycol) (PEG).14

The requirements for this study were to synthesize 50 mg quantities of each acylsemicarbazide analogue. Moreover, we wished to avoid the developmental studies required for a SPOS approach, and consequently we opted to use a solution-phase parallel synthesis of the library. The acylsemicarbazide targets were observed during the early part of our investigations to have low solubility, and we therefore elected to use relatively straightforward precipitation from solution and filtration for product isolation. The products isolated in this manner did not require subsequent purification.

Acylicsemicarbazides can be prepared by either reacting a hydrazide with dialkylcarbamoyl chloride,15 or reacting an acid chloride with a semicarbazide.16 In the first case toxic phosgene has to be used to prepare the dialkylcarbamoyl chloride, and in the second case, thionyl chloride has to be used to make the acid chloride. Both thionyl chloride and the acid chlorides can be difficult to handle and are water sensitive. As a result we wished to avoid the
use of these methods. Initially, we envisioned two possible routes to the semicarbazides. The first was to use carbamoylimidazolium salts, which we have previously shown can be used for the synthesis of ureas, thoureas, carbamates, and amides. Unfortunately, hydrazides proved to be rather unreactive towards the imidazolium salts. Even with the use of strong bases such as n-BuLi or NaHMDS, to deprotonate the hydrazides, product yields were poor and chromatographic purification was required, which was not conducive to application in a parallel synthesis. As a result we have used an alternative approach, reacting hydrazides with N,N'-carbamoylimidazole (CDI) to generate 1,3,4-oxadiazol-2-one intermediates, which are then ring-opened with an amine to give the required acylsemicarbazides (Table 1). The formation of 2 using the CDI cyclization conditions employ less toxic reagents and are more amenable to parallel synthesis than other methods, such as using trichloromethylchloroformate or phosgene. The use of the CDI protocol has not been previously applied to the preparation of 4.

Refluxing 2-thienylhydrazide 1b in THF with 1.1 equivalents of CDI overnight afforded the 1,3,4-oxadiazol-2-one 2b in good yield (80%). At room temperature, the yield was a modest 54% after 1 hour and 65% after 16 hours. Next, the conditions for the nucleophilic ring opening of 2b were investigated using pyrrolidine 3A as a test substrate to give acylsemicarbazide 4Ab. Initially, 1.05 equivalents of 3A at 0.3 M dilution in various solvents was examined. The use of CH₂Cl₂ as solvent resulted in the lowest yields of 4Ab, (only 20%), while THF, MeCN, DME, DMF, and DMSO gave comparable results and moderate yields (61–77%). Although the yields of 4Ab in DMF and DMSO were good, the product was partially soluble in DMF and completely soluble in DMSO, which made purification more problematic, and simple filtration was not viable without serious loss of product. THF was therefore chosen as a suitable solvent since it gave good yields, with the products showing limited solubility. Moreover, since the first reaction was carried out in THF, this would allow for the same solvent to be used for both steps. The addition of Et₃N as a base did not affect the yield significantly. Increasing the amount of the amine to two equivalents or raising the temperature to 50 °C increased the yield of 4Ab to above 90%. However, it was found that running the reaction at a higher concentration of 0.6 M gave the same results. Finally, when the formation of the 1,3,4-oxadiazol-2-one and subsequent ring opening with the amine was carried out in a one-pot protocol, the overall yield for 4Ab was 87%. This was an im-

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Table 1 One-Pot Synthesis of Acylsemicarbazides

- Reaction was carried out using a single-pot procedure where 1 (1 equiv) and CDI (1.1 equiv) were stirred in THF for 6 h at r.t., then amine 3 (1.05 equiv) was added and the reaction stirred at r.t. for 2 d. Products were isolated via filtration, and unless otherwise indicated, were not further purified.
- Ring opening of the oxadiazole 2 was carried out at reflux for 2 d.
- Ring opening of the oxadiazole 2 was carried out at 90 °C in chlorobenzene for 2 d.
- Isolated yield following column chromatography.
provenement relative to the best-case scenario obtained using a stepwise protocol of 76%. This also had the advantage of being a more straightforward procedure for reaction set-up, requiring minimal work-up procedures, factors which are desirable for parallel synthesis.

Optimized reaction conditions for the library synthesis used the hydrazides 1 with 1.1 equivalents of CDI at room temperature for six hours, followed by the addition of 1.05 equivalents of the amines 3. Stirring the resulting reaction mixture for two days gave the desired acylsemicarbazides 4 in good yields for the two steps (Table 1).

Conveniently, most of the acylsemicarbazides 4 were insoluble in THF and precipitated out of solution, allowing for easy isolation by filtration. The acylsemicarbazides isolated in this manner showed excellent purity by 1H and 13C NMR, greater than 95%, and were assayed for activity without further purification. The soluble acylsemicarbazides (4EA, 4EE, 4GE, 4HA, 4HB and 4HE) were purified by chromatography. Unfortunately, the diallyl amine and methyl aniline reacted in moderate yields in refluxing THF at room temperature for six hours, followed by the addition of 1.05 equivalents of CDI at room temperature for further days, afforded the products 6 in acceptable yields (Table 1). The N-methylaniline reacted in moderate yields in refluxing THF.

Finally, we attempted to make several acylthiosemicarbazide analogues using N,N'-thiocarbonyldiimidazole (TCDI). Reaction of 5-chloro-2-thiophenehydrazide (1d) with TCDI in refluxing THF, gave low yields of the 1,3,4-oxadiazol-2-thione (5). The isolated yields were 15% after one day and 52% after three days, which is perhaps not surprising as this reaction is usually carried out in refluxing EtOH using CS2 in the presence of KOH. However, the use of a one-pot reaction, in which the TCDI was reacted with the hydrazide in refluxing THF for one day, followed by the addition of the amine and stirring for further three days, afforded the products 6 in acceptable yields (Table 2). Unfortunately, the products did not precipitate out cleanly and column chromatography was necessary in all cases.

In summary, acylsemicarbazides can be synthesized using a simple, two step protocol using a precipitation for purification. The protocol proceeds through the reaction of hydrazides with CDI to generate 1,3,4-oxadiazole-2-one intermediates, which are then opened in situ with amines. In principle, this parallel synthesis method could be modified by using other nucleophiles to attack the intermediate 1,3,4-oxadiazole-2-ones. A small library of acylsemicarbazides was evaluated against a broad panel of assays for crop protection. These included plant growth regulatory, herbicidal, insecticidal, fungicidal and phytotoxicity assays. Several compounds including 4BD, 4CB and 4EB had moderate activity in primary and secondary rhizoctonia in vitro fungicidal assays, whereas compounds 4DD and 4DE had moderate activity in a primary botrytis in vitro fungicidal assay. In addition, compounds 4BE and 4GD showed modest activity in primary and secondary corn rootworm insecticidal assays. Several compounds, including 4EC, 4CC, 4CD, 4DA and 4EC had activity in primary and secondary diamondback moth insecticidal assays.

### Table 2: One-Pot Synthesis of Acylthiosemicarbazides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acylthiosemicarbazides</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
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<td>3</td>
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<td>6e</td>
<td>69</td>
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<tr>
<td>6</td>
<td>6f</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>6g</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>6h</td>
<td>63</td>
</tr>
</tbody>
</table>

*a Reaction was carried out using a single-pot procedure where 1d (1 equiv) and TCDI (1.1 equiv) were refluxed in THF for 24 h, then the reaction mixture was cooled and amine 3 (1.05 equiv) was added and the reaction was stirred at r.t. for further 3 d.

*b Isolated yield following column chromatography.

All commercial reagents were used as received (Aldrich Chemical Co., Fischer Scientific Ltd. and Trans World Chemicals Inc.). THF was distilled from sodium metal/benzophenone under N2. 1H NMR and 13C NMR spectra were recorded on a Mercury 300 NMR spectrometer at 300 MHz and 75 MHz, respectively. Low resolution electron impact (EI) mass spectra were obtained using a Bell and Howell 21-490 spectrometer, and high resolution spectra were recorded on an AEI MS3074 mass spectrometer. FT-IR spectra were recorded on a Perkin-Elmer Spectrum 1000, with samples loaded as
thin films on NaCl plates. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

5-[2(Thiophen-3-yl)oxadiazol-2-one (2b)\(^{16b}\)]

To a suspension of CDI (1.88 g, 11.6 mmol, 1 equiv) in anhyd THF (15.0 mL) was added 2-thiophenylhydrazide (1.50 g, 10.6 mmol, 1 equiv) and the reaction mixture was refluxed overnight. The solvent was removed and the crude yellow oil was dissolved in CH\(_2\)Cl\(_2\), washed with H\(_2\)O, brine, dried (MgSO\(_4\)), and concentrated. Column chromatography (Rf 0.5; hexane–EtOAc, 7:3) of the crude product gave 2b as a white solid (1.42 g, 80%); mp 130–135 °C.

IR (thin film): 3213, 1772, 1617, 1446, 1358, 1233, 1094, 1016, 953 cm\(^{-1}\).

\( ^{1}H\) NMR (CD\(_3\)OD): \( \delta = 9.70 \) (s, 1 H), 7.61 (dd, \( J = 3.5 \), 1.0 Hz, 1 H), 7.51 (dd, \( J = 5.0 \), 1.0 Hz, 1 H), 7.12–7.14 (m, 1 H).

\( ^{13}C\) NMR (CD\(_3\)OD): \( \delta = 154.9 \), 152.2, 130.0, 129.7, 128.2, 125.4.

MS (EI): \([M+]^+\) = 311 (40) \([M]^+\), 240 (77), 196 (37), 183 (39), 155 (27), 98 (100).

HRMS (EI): \( m/z [M^{+}] \) calcd for C\(_{10}\)H\(_{12}\)BrN\(_3\)O\(_3\): 311.0269; found: 311.0263.

**Parallel Synthesis of a Library of Acylsemicarbazides**

**Pyrrolidine-1-carboxylic Acid N\(^{+}\)-(3-Bromobenzoyl)hydrazide (4Ac)**

Yield: 62%; white solid; mp 208 °C.

IR (thin film): 3198, 3017, 1627, 1563, 1532, 1400, 1329, 1230 cm\(^{-1}\).

\( ^{1}H\) NMR (CD\(_3\)OD): \( \delta = 8.08 \) (s, 1 H), 7.88 (d, \( J = 8.5 \) Hz, 1 H), 7.74–7.77 (m, 1 H), 7.44 (t, \( J = 8.0 \) Hz, 1 H), 3.38–3.48 (m, 4 H), 1.95–2.00 (m, 4 H).

\( ^{13}C\) NMR (CD\(_3\)OD): \( \delta = 168.5 \), 158.2, 136.3, 131.9, 131.6, 127.6, 123.6, 47.0, 26.5.

MS (EI): \( m/z [M^{+}] \) calcd for C\(_{10}\)H\(_{12}\)BrN\(_3\)O\(_3\): 311.0269; found: 311.0263.

4-Phenylpiperazine-1-carboxylic Acid N\(^{+}\)-(5-Bromofuran-2-carbonyl)hydrazide (4Ba)

Yield: 83%; white solid.

IR (thin film): 3238, 1634, 1538, 1495, 1416, 1265, 1233 cm\(^{-1}\).

\( ^{1}H\) NMR (CD\(_3\)OD): \( \delta = 7.81 \) (dd, \( J = 3.5 \), 1.0 Hz, 1 H), 7.73 (dd, \( J = 5.0 \), 1.0 Hz, 1 H), 7.25–7.31 (m, 2 H), 7.17 (dd, \( J = 5.0 \), 4.0 Hz, 1 H), 7.00–7.04 (m, 2 H), 6.90 (t, \( J = 7.5 \) Hz, 1 H), 3.67 (t, \( J = 5.0 \) Hz, 4 H), 3.22 (t, \( J = 5.0 \) Hz, 4 H).

4-Phenylpiperazine-1-carboxylic Acid N\(^{+}\)-(Thiophene-2-carbonyl)hydrazide (4Bb)

Yield: 45%; white solid; mp 189 °C.

IR (thin film): 3213, 1772, 1617, 1446, 1358, 1094, 1016, 953 cm\(^{-1}\).

\( ^{1}H\) NMR (CD\(_3\)OD): \( \delta = 7.63 \) (d, \( J = 4.0 \) Hz, 1 H), 7.25–7.30 (m, 2 H), 7.01–7.04 (m, 2 H), 6.89 (t, \( J = 7.0 \) Hz, 1 H), 3.67 (t, \( J = 5.0 \) Hz, 4 H), 3.21 (t, \( J = 5.0 \) Hz, 4 H).

4-Phenylpiperazine-1-carboxylic Acid N\(^{+}\)-(3-Bromothiophene-2-carbonyl)hydrazide (4Bc)

Yield: 76%; white solid; mp 122 °C.

IR (thin film): 3213, 1772, 1617, 1446, 1358, 1094, 1016, 953 cm\(^{-1}\).

\( ^{1}H\) NMR (CD\(_3\)OD): \( \delta = 7.70 \) (d, \( J = 4.0 \) Hz, 1 H), 7.20–7.23 (m, 3 H), 7.01–7.04 (m, 2 H), 6.90 (t, \( J = 7.5 \) Hz, 1 H), 3.67 (t, \( J = 5.0 \) Hz, 4 H), 3.21 (t, \( J = 5.0 \) Hz, 4 H).

4-Phenylpiperazine-1-carboxylic Acid N\(^{+}\)-(5-Chlorothiophene-2-carbonyl)hydrazide (4Bd)

Yield: 74%; white solid.

IR (thin film): 3213, 1772, 1617, 1446, 1358, 1094, 1016, 953 cm\(^{-1}\).

\( ^{1}H\) NMR (CD\(_3\)OD): \( \delta = 7.63 \) (d, \( J = 4.0 \) Hz, 1 H), 7.25–7.30 (m, 2 H), 7.01–7.04 (m, 3 H), 6.89 (t, \( J = 7.0 \) Hz, 1 H), 3.67 (t, \( J = 5.0 \) Hz, 4 H), 3.21 (t, \( J = 5.0 \) Hz, 4 H).

4-Phenylpiperazine-1-carboxylic Acid N\(^{\prime}\)-(3-Bromobenzoyl)hydrazide (4Be)
Yield: 82\%; white solid.
\(^1\)H NMR (CD\(_3\)OD): \(\delta = 8.09\) (m, 1 H), 7.89 (m, 1 H), 7.76 (m, 1 H), 7.44 (t, \(J = 8.0\) Hz, 1 H), 7.28 (m, 2 H), 7.04 (m, 2 H), 6.90 (t, \(J = 7.5\) Hz, 1 H), 3.69 (t, \(J = 5.0\) Hz, 4 H), 3.23 (t, \(J = 5.0\) Hz, 4 H).

Morpholine-4-carboxylic Acid N\(^{\prime}\)-(5-Bromofuran-2-carbonyl)hydrazide (4Ca)
Yield: 67\%; white solid.
\(^1\)H NMR (CD\(_3\)OD): \(\delta = 7.22\) (d, \(J = 3.5\) Hz, 1 H), 6.67 (d, \(J = 2.5\) Hz, 1 H), 3.72 (t, \(J = 5.0\) Hz, 4 H), 3.48 (t, \(J = 5.0\) Hz, 4 H).

Morpholine-4-carboxylic Acid N\(^{\prime}\)-(Thiophene-2-carbonyl)hydrazide (4Cb)
Yield: 67\%; white solid.
\(^1\)H NMR (CD\(_3\)OD): \(\delta = 7.65\) (dd, \(J = 3.5\), 1.0 Hz, 1 H), 7.58 (dd, \(J = 5.0\), 1.0 Hz, 1 H), 7.02 (dd, \(J = 5.0\), 4.0 Hz, 1 H), 3.57 (t, \(J = 5.0\) Hz, 4 H), 3.34 (t, \(J = 5.0\) Hz, 4 H).

Morpholine-4-carboxylic Acid N\(^{\prime}\)-(5-Bromothiophene-2-carbonyl)hydrazide (4Cc)
Yield: 66\%; white solid.
\(^1\)H NMR (CD\(_3\)OD): \(\delta = 7.43\) (d, \(J = 4.0\) Hz, 1 H), 7.06 (d, \(J = 4.0\) Hz, 1 H), 3.58 (t, \(J = 5.0\) Hz, 4 H), 3.34 (t, \(J = 5.0\) Hz, 4 H).

Morpholine-4-carboxylic Acid N\(^{\prime}\)-(5-Chlorothiophene-2-carbonyl)hydrazide (4Cd)
Yield: 60\%; white solid; mp 203 °C.
IR (thin film): 3215, 3021, 1625, 1557, 1424, 1264, 1119, 1001 cm\(^{-1}\).
\(^1\)H NMR (CD\(_3\)OD): \(\delta = 7.62\) (d, \(J = 4.0\) Hz, 1 H), 7.08 (d, \(J = 4.0\) Hz, 1 H), 3.72 (t, \(J = 5.0\) Hz, 4 H), 3.48 (t, \(J = 5.0\) Hz, 4 H).

[The rest of the text follows with similar information for each compound, including NMR and IR data, synthesis details, and yields.]
Yield: 90%; white solid.

IR (thin film): 3217, 2973, 1626, 1548, 1521, 1425, 1278, 1158 cm⁻¹.

1H NMR (CD3OD): δ = 7.59 (d, J = 4.0 Hz, 1 H), 7.00 (d, J = 4.0 Hz, 1 H), 3.30–3.37 (m, 4 H), 1.17 (t, J = 7.0 Hz, 6 H).

13C NMR (CD3OD): δ = 162.2, 157.9, 135.9, 135.5, 129.0, 127.5, 41.3, 12.7.

MS (EI): m/z (%) = 275 (18) [M⁺], 202 (81), 158 (33), 145 (56), 100 (100), 72 (65).


Synthesis of Semicarbazides 4Ga–4Ge; General Procedure
To a suspension of CDI (0.770 mmol, 1.1 equiv) in anhyd THF (1.5 mL) was added the hydrazide I (0.700 mmol, 1 equiv) and the reaction mixture was stirred at r.t. for 6 h. At that time N-methylaniline (0.735 mmol, 1.05 equiv) was added and the reaction was stirred at 80 °C for 2 d. The precipitated product was filtered off and dried to give 4Ga–4Ge. Purity by 1H NMR was greater than 95%.

4-Phenyl-4-methyl-1-(5-bromofuran-2-carbonyl)semicarbazide (4Ga)
Yield: 38%; white solid.

1H NMR (CD3OD): δ = 7.33–7.46 (m, 5 H), 7.15 (d, J = 3.5 Hz, 1 H), 6.60 (d, J = 3.5 Hz, 1 H), 3.28 (s, 3 H).

Yield: 60%; white solid.

1H NMR (CD3OD): δ = 7.33–7.46 (m, 5 H), 7.15 (d, J = 3.5 Hz, 1 H), 6.60 (d, J = 3.5 Hz, 1 H), 3.28 (s, 3 H).


4-Phenyl-4-methyl-1-(5-bromothiophene-2-carbonyl)semicarbazide (4Gb)
Yield: 57%; white solid; mp 75–78 °C.

IR (thin film): 3241, 3086, 1650, 1537, 1494, 1353, 1296, 1134 cm⁻¹.

1H NMR (CD3OD): δ = 7.75 (dd, J = 4.0, 1.0 Hz, 1 H), 7.66 (dd, J = 5.0, 1.0 Hz, 1 H), 7.32–7.47 (m, 5 H), 7.09 (dd, J = 5.0, 4.0 Hz, 1 H), 3.27 (s, 3 H).

13C NMR (DMSO-d₆): δ = 163.2, 158.1, 142.9, 136.4, 130.1, 129.7, 129.3, 127.8, 127.1, 137.2.

MS (EI): m/z (%) = 275 (5) [M⁺], 168 (47), 134 (29), 124 (28), 107 (100).


4-Phenyl-4-methyl-1-(thiophene-2-carbonyl)semicarbazide (4Gd)
Yield: 60%; white solid.

1H NMR (CD3OD): δ = 7.51 (d, J = 4.0 Hz, 1 H), 7.32–7.47 (m, 5 H), 7.10 (d, J = 4.0 Hz, 1 H), 3.27 (s, 3 H).

IR (thin film): 3235, 3020, 1650, 1550, 1494, 1426, 1332, 1135 cm⁻¹.

1H NMR (CD3OD): δ = 7.57 (d, J = 4.0 Hz, 1 H), 7.32–7.46 (m, 5 H), 6.94 (d, J = 4.0 Hz, 1 H), 3.27 (s, 3 H).

13C NMR (DMSO-d₆): δ = 162.0, 158.0, 142.7, 135.8, 129.8, 129.2, 127.6, 127.6, 127.1, 37.3.

MS (EI): m/z (%) = 309 (9) [M⁺], 202 (59), 158 (32), 145 (47), 134 (47), 107 (100).

4-Phenyl-4-methyl-1-(3-bromobenzoyl)semicarbazide (4Ge)
Yield: 8%; clear oil; purified by column chromatography, Rf 0.42 (hexane–EtOAc, 1:1).

1H NMR (CD3OD): δ = 8.01 (t, J = 1.5 Hz, 1 H), 7.79–7.83 (m, 1 H), 7.68–7.72 (m, 1 H), 7.32–7.49 (m, 6 H), 3.29 (s, 3 H).

5-Chlorothiophene-2-carboxylic Acid
Yield: 69%; beige solid; purified by column chromatography, Rf 0.29 (hexane–EtOAc, 1:1).

IR (thin film): 3220, 3022, 1626, 1558, 1540, 1426, 1340, 1260, 927 cm⁻¹.

HRMS (EI): m/z (%) = 345 (5) [M⁺], 264 (19), 248 (98), 202 (49), 189 (74), 124 (100).


5-Chlorothiophene-2-carboxylic Acid N'-Pyrrolidine-1-carbothioyl)hydrazide (6a)
Yield: 83%; white solid; Rf 0.22 (hexane–EtOAc, 1:1).

1H NMR (CD3OD): δ = 7.64 (d, J = 4.0 Hz, 1 H), 7.04 (d, J = 4.0 Hz, 1 H), 3.65 (br s, 4 H), 2.02 (br s, 4 H).

5-Chlorothiophene-2-carboxylic Acid N’-(4-Phenylpiperazine-1-carbothioyl)hydrazide (6b)
Yield: 30%; white solid; Rf 0.11 (hexane–EtOAc, 7:3).

1H NMR (CD3OD): δ = 7.65 (d, J = 4.0 Hz, 1 H), 7.22–7.28 (m, 2 H), 7.06 (d, J = 4.0 Hz, 1 H), 6.97–7.00 (m, 2 H), 6.85 (t, J = 7.5 Hz, 1 H), 4.08 (t, J = 5.0 Hz, 4 H), 3.72 (t, J = 5.0 Hz, 4 H).

5-Chlorothiophene-2-carboxylic Acid N’-(Morpholine-4-carbothioyl)hydrazide (6c)
Yield: 70%; off-white solid; Rf 0.18 (hexane–EtOAc, 1:1).

1H NMR (CD3OD): δ = 7.65 (d, J = 4.0 Hz, 1 H), 7.06 (d, J = 4.0 Hz, 1 H), 3.90 (t, J = 4.5 Hz, 4 H), 3.72 (t, J = 4.5 Hz, 4 H).

5-Chlorothiophene-2-carboxylic Acid N’-(3,4-Dihydro-1H-isoquinoline-2-carbothioyl)hydrazide (6d)
Yield: 65%; beige solid; Rf 0.25 (hexane–EtOAc, 7:3).

1H NMR (CD3OD): δ = 7.66 (d, J = 4.0 Hz, 1 H), 7.19–7.21 (m, 4 H), 7.05 (d, J = 4.0 Hz, 1 H), 5.00 (s, 2 H), 4.04 (t, J = 6.0 Hz, 2 H), 2.97 (t, J = 6.0 Hz, 2 H).

4,4-Diethyl-1-(5-chlorothiophene-2-carbonyl)thiosemicarbazide (6e)
Yield: 69%; beige solid; Rf 0.30 (hexane–EtOAc, 7:3).

1H NMR (CD3OD): δ = 7.64 (d, J = 4.0 Hz, 1 H), 7.04 (d, J = 4.0 Hz, 1 H), 3.70–3.77 (m, 4 H), 1.24 (t, J = 7.0 Hz, 6 H).

Synthesis of Thiosemicarbazides 6; General Procedure
To a suspension of TCDI (0.770 mmol, 1.1 equiv) in anhyd THF (1.5 mL) was added the hydrazide 1 (0.700 mmol, 1 equiv) and the reaction mixture was stirred at r.t. for 24 h. The reaction mixture was cooled, the amine (0.735 mmol, 1.05 equiv) was added and the reaction mixture was stirred for a further 3 d. The crude reaction mixture was diluted with EtOAc and washed with 1 N HCl, H2O, brine, dried (MgSO4), filtered and concentrated. Purification by column chromatography afforded the desired products 6.

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Synthesis of Semicarbazides 4Ha–4He; General Procedure
To a suspension of CDI (0.770 mmol, 1 equiv) in anhyd THF (1.5 mL) was added the hydrazide 1 (0.700 mmol, 1 equiv) and the reaction mixture was stirred at r.t. for 6 h. The solvent was then removed in vacuo. The residue was dissolved in chlorobenzene (1.0 mL) and diallylamine (0.735 mmol, 1.05 equiv) was added and the reaction mixture was stirred at 90 °C for 2 d. The products 4Ha–4He were isolated either by filtration or column chromatography.

Yield: 59%; white solid; purified by column chromatography, Rf 0.38 (hexane–EtOAc, 1:1).

IR (thin film): 3205, 3009, 1622, 1558, 1402, 1339, 1257, 923 cm⁻¹.

HRMS (EI): m/z (%) = 345 (5) [M⁺], 264 (19), 248 (98), 202 (49), 189 (74), 124 (100).


Yield: 65%; white solid; purified by column chromatography, Rf 0.45 (hexane–EtOAc, 1:1).

5-Chlorothiophene-2-carboxylic Acid N’-(Pyrrolidine-1-carbothioyl)hydrazide (6a)
Yield: 83%; white solid; Rf 0.22 (hexane–EtOAc, 1:1).

1H NMR (CD3OD): δ = 7.64 (d, J = 4.0 Hz, 1 H), 7.04 (d, J = 4.0 Hz, 1 H), 3.65 (br s, 4 H), 2.02 (br s, 4 H).

5-Chlorothiophene-2-carboxylic Acid N’-(4-Phenylpiperazine-1-carbothioyl)hydrazide (6b)
Yield: 30%; white solid; Rf 0.11 (hexane–EtOAc, 7:3).

1H NMR (CD3OD): δ = 7.65 (d, J = 4.0 Hz, 1 H), 7.22–7.28 (m, 2 H), 7.06 (d, J = 4.0 Hz, 1 H), 6.97–7.00 (m, 2 H), 6.85 (t, J = 7.5 Hz, 1 H), 4.08 (t, J = 5.0 Hz, 4 H), 3.72 (t, J = 5.0 Hz, 4 H).

5-Chlorothiophene-2-carboxylic Acid N’-(Morpholine-4-carbothioyl)hydrazide (6c)
Yield: 70%; off-white solid; Rf 0.18 (hexane–EtOAc, 1:1).

1H NMR (CD3OD): δ = 7.65 (d, J = 4.0 Hz, 1 H), 7.06 (d, J = 4.0 Hz, 1 H), 3.90 (t, J = 4.5 Hz, 4 H), 3.72 (t, J = 4.5 Hz, 4 H).

5-Chlorothiophene-2-carboxylic Acid N’-(3,4-Dihydro-1H-isoquinoline-2-carbothioyl)hydrazide (6d)
Yield: 65%; beige solid; Rf 0.25 (hexane–EtOAc, 7:3).

1H NMR (CD3OD): δ = 7.66 (d, J = 4.0 Hz, 1 H), 7.19–7.21 (m, 4 H), 7.05 (d, J = 4.0 Hz, 1 H), 5.00 (s, 2 H), 4.04 (t, J = 6.0 Hz, 2 H), 2.97 (t, J = 6.0 Hz, 2 H).

4,4-Diethyl-1-(5-chlorothiophene-2-carbonyl)thiosemicarbazide (6e)
Yield: 69%; beige solid; Rf 0.30 (hexane–EtOAc, 7:3).

1H NMR (CD3OD): δ = 7.64 (d, J = 4.0 Hz, 1 H), 7.04 (d, J = 4.0 Hz, 1 H), 3.70–3.77 (m, 4 H), 1.24 (t, J = 7.0 Hz, 6 H).
4-Benzyl-4-methyl-1-(5-chlorothiophene-2-carbonyl)thiosemicarbazide (6f)
Yield: 22%; yellow solid; mp 200–203 °C; 

**References**


(18) For examples of the use of CDI in parallel synthesis, see:


(24) Other nucleophiles that are known to ring-open 1,3,4-oxadiazole-2-ones via nucleophilic attack include hydrazines and thiols, for example, see ref. 20 and: