Bioorganic & Medicinal Chemistry 25 (2017) 6218–6223

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

A continuous flow synthesis and derivatization of 1,2,4-thiadiazoles

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ARTICLE INFO

Article history:
Received 2 December 2016
Revised 12 January 2017
Accepted 14 January 2017
Available online 23 January 2017

Keywords:
Flow synthesis
Microreactors
Heterocycles
Thiadiazoles
Medicinal chemistry

ABSTRACT

A continuous flow process is presented that enables the efficient synthesis and derivatization of 1,2,4-thiadiazole heterocycles. Special attention was given to the safe handling of the versatile yet hazardous trichloromethane sulfenylchloride reagent including its in-line quenching in order to eliminate malodourous and corrosive by-products. Based on this flow method gram quantities of 5-chloro-3-phenyl-1,2,4-thiadiazole were safely prepared allowing for further elaboration of this valuable building block by reaction with different nitrogen-, sulfur- and oxygen-based nucleophiles. This synthetic approach was subsequently applied to generate a series of bromophenyl-5-chloro-1,2,4-thiadiazoles providing a valuable entry towards further structural diversification on this important heterocyclic scaffold.

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1. Introduction

Thiadiazoles represent a unique subclass of bioactive five-membered aromatic heterocycles containing one sulfur and two nitrogen atoms.[1–4] The presence of these heteroatoms increases both the membrane permeability as well as the ability to act as versatile hydrogen bond acceptors. Due to the spacial similarity of vinyl groups to ring embedded sulfur atoms thiadiazoles can be considered isosteres of diazines[5,6] adding to their potential to serve as fragments of bioactive structures.[7–10] Thiadiazoles can occur in four distinct regioisomeric forms (**1**–**4**) enriching their structural diversity with respect to local polarization and vector space occupied by both carbon bound substituents R_1 and R_2 (Fig. 1).

Amongst the possible thiadiazole isoforms the 1,2,4-thiadiazole scaffold is an important structure as it resembles the ubiquitous pyrimidine moiety. The synthesis of 1,2,4-thiadiazoles can be accomplished by a variety of methods including oxidative ring closure,[11,12] multicomponent reactions[13] or [3 + 2]-cycloadditions.[14] A further option which is more amenable to subsequent functionalization on the heterocyclic scaffold is based on reacting various amidines with trichloromethane sulfenylchloride (**5**, Scheme 1).[15] Although very versatile this reagent poses several safety risks as it is unstable and readily decomposes into highly corrosive and malodorous species.[16] In order to mitigate these hazards we decided to harness the benefits of flow reactor technology[17–26] to study the safe and efficient use of trichloromethane sulfenylchloride en route to 5-chloro-1,2,4-thiadiazoles that would allow further functionalization reactions to take place at the activated 5-position of this scaffold.

2. Results and discussion

In order to safely employ trichloromethane sulfenylchloride we opted to utilize a Vapourtec R-series flow system[27] as it is amenable to using either the injection sample loops (for small scale reactions) or pumping directly from reagent bottles (for scale up operations).

Stock solutions of trichloromethane sulfenylchloride (**5**, 0.45 M in EtOAc) and hydrated benzamidine hydrochloride salt (**6**, 0.4 M in 1.5 M aqueous NaOH) were freshly prepared before each set of experiments and used up within 2–3 h. As depicted in Scheme 1 the reagent solutions were loaded into the sample loops (PTFE, 2–5 mL each) and subsequently pumped at equal flow rates to unite at a T-piece (PEEK, 1.3 mm ID). The initial mixing resulted in an emulsion that then separated into individual droplets due to the biphasic nature of the solvent system. This stream was then directed through two tubular coiled reactors (PTFE, 10 mL each, ambient temperature, no active cooling) followed by a 75 psi back-pressure regulator prior to be collected into a round-bottom flask.

Using this set-up allowed us to rapidly screen a selection of conditions and quickly confirm the viability of preparing the desired 5-chloro-1,2,4-thiadiazole building block **7** in a short residence time of only 5 min with yields up to 80%. Importantly the improved heat transfer offered by this flow approach meant that the reaction can be performed at ambient temperature without decomposition or run-away phenomena being observed. Although the desired

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http://dx.doi.org/10.1016/j.bmc.2017.01.022
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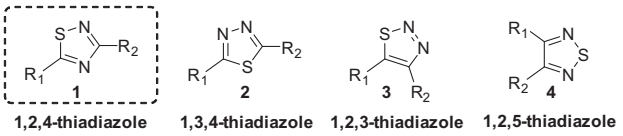
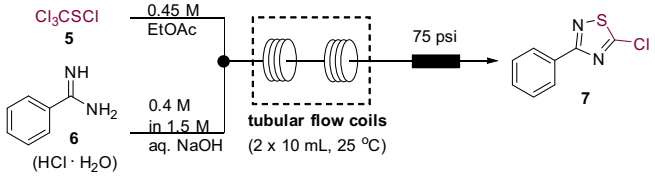


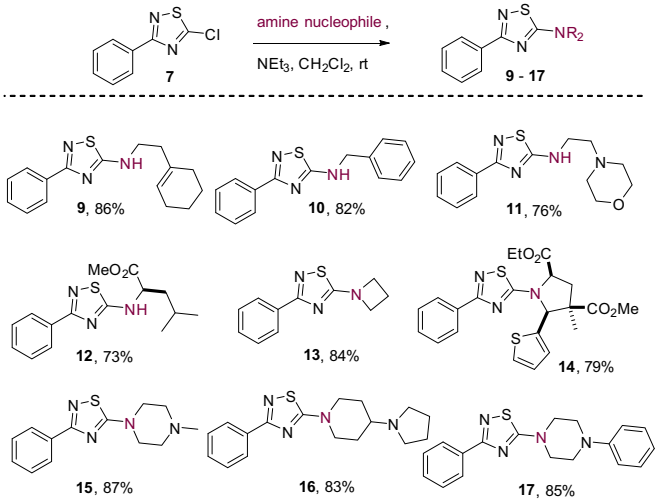
Figure 1. Regioisomerism of thiadiazoles (**1**–**4**).



Scheme 1. Flow reactor set-up.

reaction reaches completion in <5 min we elected to use a residence time of 30 min in order to further ensure complete hydrolysis of any residual reagent **5** in addition to any of its hazardous by-products in the alkaline aqueous co-solvent. This is very selective as the desired product **7** resides preferentially in the organic phase which minimizes its hydrolysis to the corresponding 5-hydroxy derivative (**8**). This is more difficult to achieve in a batch process showcasing another benefit of this flow process. Encouraged by these results we decided to test the scale up of **7** by processing a 20-fold amount of starting materials in an analogous fashion (20 mmol scale). Pleasingly this directly translated into an efficient access to multi-gram quantities of the desired 5-chloro-1,2,4-thiadiazole **7** which was isolated in pure form after aqueous extraction and filtration over a short plug of silica with hexanes as the eluent yielding 3.25 g of **7** (83%).

With sufficient quantities of compound **7** in hand we proceeded to study its functionalization via reaction with different nucleophiles in a simple parallel batch process. We therefore dissolved aliquots of **7** in CH_2Cl_2 (1.0 mmol, 2.5 M) and added the desired nucleophile (1.1 equiv.) and triethylamine as base (1.1 equiv.). The reactions were stirred at 25 °C until complete conversion of **7** was indicated by tlc (typically 2–8 h) followed by evaporation and purification by silica gel chromatography. Pleasingly, this approach allowed us to quickly generate a small selection of reaction products based on various nitrogen nucleophiles including aliphatic as well as variable cyclic amine species (Scheme 2).



Scheme 2. Functionalization of **7** with amine nucleophiles.

Furthermore, we established that substituted thioimidazoles obtained via a Marckwald multicomponent reaction[28] are equally competent nucleophiles analogously delivering interesting sulfide linked architectures in good yield (Fig. 2). Finally, we found that 5-phenoxy substituted 1,2,4-thiadiazoles can be generated by treating a solution of **7** (0.5 M, THF) at room temperature with phenols in the presence of polymer-substituted BEMP as base leading to the clean and high-yielding formation of the desired adduct **21** (Fig. 2).

The connectivity of selected reaction products (**13** and **20**) was confirmed by single crystal X-ray diffraction experiments (Figure 3). This also revealed an interesting π-stacking phenomenon between the thiadiazole ring and a nearby aryl moiety in the case of sulfide linked entities (e.g. **20**).

In an extension of our studies we decided to investigate the formation of 5-chloro-1,2,4-thiadiazole building blocks that would enable functionalization in a bidirectional sense. To this end we opted to incorporate bromo-substituents located at different positions of the phenyl moiety enabling future diversification by means of metal mediated amination or cross-coupling reactions (Fig. 4).

The required bromophenylamidine substrates (**22**–**24**) were prepared by reacting ortho-, meta- and para-bromobenzonitrile (0.5 M, THF) with a solution of NaHMDS (1.5 M, 1.2 equiv., THF, 1 h, rt) rendering after treatment with aqueous hydrochloric acid the desired bromophenylamidine HCl-salts **22**–**24** (see experimental section for full details). Having gained a quick access to these substrates we applied them towards the flow-synthesis of the corresponding thiadiazole derivatives (Scheme 3). In order to avoid any potential solubility issues we modified the initial set-up by first mixing trichloromethane sulfenylchloride (**5**, stream 1, 0.45 M, EtOAc) with the bromophenylamidine HCl-salt (**22**–**24**, stream 2, 0.4 M, H_2O) prior to adding a stream containing NaOH (stream 3, 1.5 M, H_2O). The resulting biphasic reaction mixture was then again directed through two flow coils maintained at

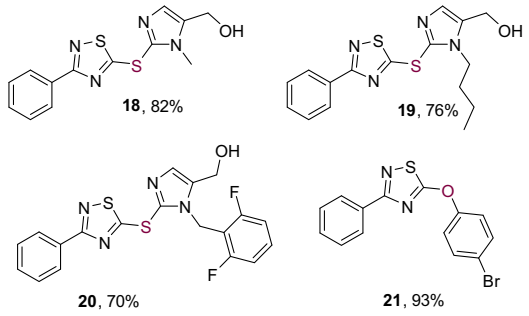


Figure 2. Structures of sulfur- and oxygen-linked products 18–**21.**

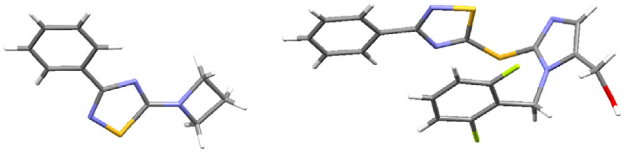


Figure 3. X-ray crystal structures of **13** (left) and **20** (right).

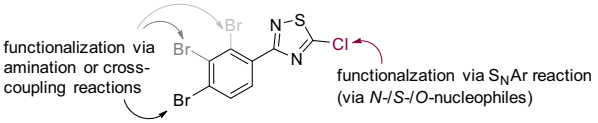
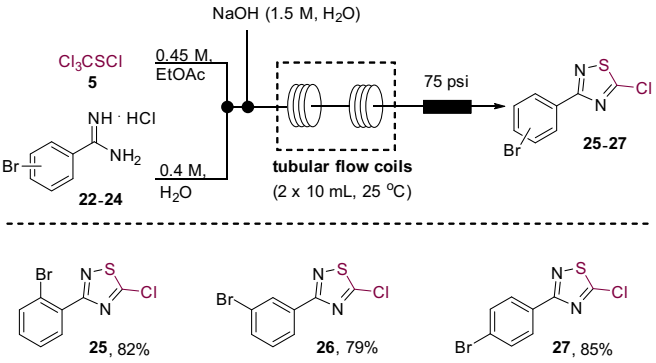


Figure 4. Key scaffold for bidirectional diversification.



Scheme 3. Flow synthesis of thiadiazoles **25**–**27.**

ambient temperature (residence time 30 min) before being collected and purified by aqueous work-up and silica column chromatography. Pleasingly this approach enabled the rapid and high yielding generation of three regioisomeric building blocks (**25**–**27**) that can be exploited towards expanded thiadiazole libraries.

3. Conclusion

In conclusion we have developed a flow process for converting benzamidine HCl-salts into valuable 1,2,4-thiadiazole derivatives based on safely utilizing trichloromethane sulfenylchloride as a versatile reagent. Exploiting the 5-chloro substituent we subsequently demonstrated the simple generation of a small set of 1,2,4-thiadiazole derivatives bearing different nitrogen-, sulfur- or oxygen-nucleophiles by means of efficient S_NAr reactions. Finally, we extended our methodology to also access reaction products containing a bromophenyl moiety that together with the 5-chloro functionality allows for orthogonal and regiospecific diversification of the 1,2,4-thiadiazole system.

4. Experimental protocols

4.1. General methods and materials

Unless otherwise stated, all solvents, substrates and reagents were used as purchased without further purification.

^{1}H NMR spectra were recorded on 400 MHz instruments and are reported relative to residual solvent: $CHCl_3$ (δ 7.26 ppm) or DMSO (δ 2.50 ppm). ^{13}C NMR spectra were recorded on the same instrument and are reported relative to $CHCl_3$ (δ 77.16 ppm) or DMSO (δ 39.52 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ/ ppm) (integration, multiplicity, coupling constant (Hz)). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br. s = broad singlet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shift (δ/ ppm) and multiplicity (C, CH, CH_2 or CH_3). DEPT-135, COSY, HSQC, HMBC and NOESY experiments were used in the structural assignment. IR spectra were recorded neat (ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21–70% of tallest signal) or strong (s, >71% of tallest signal). Low and high resolution mass spectrometry was performed using the indicated techniques on instruments equipped with Acquity UPLC and a lock-mass electrospray ion source. Melting points were recorded on an automated melting point system with a heating rate of 1 °C/min and are uncorrected.

4.2. Synthetic procedures

In order to synthesise 5-chloro-1,2,4-thiadiazole **7** stock solutions of **5** (0.45 M in EtOAc) and hydrated benzamidine hydrochloride salt (**6**, 0.4 M in 1.5 M aqueous NaOH) were prepared and injected into the sample loops (2–5 mL) of a Vapourtec R-series flow system. Both streams were pumped at equal flow rates (0.33 mL/min) and directed into two successive tubular flow reactors (10 mL each, rt) after being combined at a T-piece. Upon exiting the second flow reactor the combined reaction stream passed a back-pressure regulator (75 psi) before being collected into a flask. After aqueous extraction (3 × 10 mL water) the organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The organic residue was further purified by silica column chromatography using EtOAc/hexanes (5/95 to 10/90) as eluent yielding the desired thiadiazole **7** after evaporation of all volatiles as a yellow oil. Small amounts of hydrolysis product **8** were isolated as white solid.

4.2.1. 5-Chloro-3-phenyl-1,2,4-thiadiazole (7)

At 1 mmol scale: Yellow oil; yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22–8.28 (m, 2H), 7.45–7.70 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9 (C), 172.1 (C), 131.9 (C), 130.9 (CH), 128.8 (2CH), 128.1 (2CH). IR (neat, ν/cm^{-1}): 1471 (s), 1439 (s), 1319 (m), 1273 (s), 1112 (m), 1057 (s), 781 (m), 706 (s), 688 (s), 650 (m). HRMS (ES-TOF$^+$) calculated for $C_8H_6N_2ClS$ 196.9940, found 196.9941.

4.2.2. 3-Phenyl-1,2,4-thiadiazole-5-ol (8)

Isolated as a by-product. White solid; melting range: 204.6–207.0 °C; yield: 10–20%. ^{1}H NMR (400 MHz, d_6-DMSO): δ 13.41 (br s, 1H), 7.90–7.99 (m, 2H), 7.49–7.55 (m, 3H). ^{13}C NMR (101 MHz, d_6-DMSO): δ 180.0 (C), 155.1 (C), 131.8 (CH), 129.4 (2CH), 129.0 (C), 127.0 (2CH). IR (neat, ν/cm^{-1}): 2800–3200 (br), 1642 (s), 1542 (m), 1504 (m), 1463 (m), 1434 (m), 1175 (m), 919 (m), 778 (s), 733 (m), 689 (s), 593 (s), 466 (m). HRMS (ES-TOF$^+$) calculated for $C_8H_7N_2OS$ 179.0279, found 179.0282.

For derivatizing 5-chloro-3-phenyl-1,2,4-thiadiazole (**7**) with different nucleophiles a solution of **7** (1.0 equiv., 2.5 M, DCM) was prepared. The desired nucleophile (1.1 equiv.) and triethylamine (1.1 equiv.) were added to this solution. The resulting reaction mixture was stirred at 25 °C until complete consumption of the substrates was observed by tlc (2–8 h). After aqueous extraction (3 × 10 mL water) the organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness furnishing the desired product which was furthermore purified by silica column chromatography (EtOAc/hexanes 10/90 to 30/70).

4.2.3. N-(2-(Cyclohex-1-en-1-yl)ethyl)-3-phenyl-1,2,4-thiadiazole-5-amine (9)

White solid; melting range: 138.0–140.5 °C; yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13–8.18 (m, 2H), 7.39–7.45 (m, 3H), 6.32 (br s, 1H), 5.49 (br s, 1H), 3.31 (app q, J = 6.6 Hz, 2H), 2.28 (app t, J = 6.6 Hz, 2H), 1.95–2.05 (m, 2H), 1.85–1.93 (m, 2H), 1.56–1.62 (m, 2H), 1.48–1.55 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 184.5 (C), 170.0 (C), 133.5 (C), 133.3 (C), 129.9 (CH), 128.5 (2CH), 127.9 (2CH), 124.8 (CH), 44.3 (CH_2), 37.2 (CH_2), 27.7 (CH_2), 25.2 (CH_2), 22.7 (CH_2), 22.2 (CH_2). IR (neat, ν/cm^{-1}): 3235 (m), 2923 (m), 1575 (s), 1459 (m), 1426 (m), 1349 (s), 1299 (m), 1071 (m), 1017 (m), 779 (m), 703 (s), 576 (m). HRMS (ES-TOF$^+$) calculated for $C_{16}H_{20}N_3S$ 286.1378, found 286.1371.

4.2.4. N-Benzyl-3-phenyl-1,2,4-thiadiazol-5-amine (10)

White solid; melting range: 101.6–103.8 °C; yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13–8.18 (m, 2H), 7.37–7.43 (m, 3H), 7.30–7.36 (m, 5H), 6.76 (br s, 1H), 4.49 (d, J = 5.6 Hz, 2H). ^{13}C NMR

(101 MHz, $CDCl_3$): δ 184.5 (C), 169.9 (C), 136.2 (C), 133.2 (C), 129.9 (CH), 128.9 (2CH), 128.5 (2CH), 128.2 (CH), 127.9 (2CH), 127.7 (2CH), 50.5 (CH_2). IR (neat, ν/cm^{-1}): 3215 (m), 3029 (w), 1739 (w), 1559 (s), 1467 (m), 1430 (m), 1345 (s), 1217 (w), 1027 (w), 707 (s). HRMS (ES-TOF$^+$) calculated for $C_{15}H_{14}N_3S$ 268.0908, found 268.0900.

4.2.5. N-(2-Morpholinoethyl)-3-phenyl-1,2,4-thiadiazol-5-amine (11)

Colourless oil; yield: 76%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13–8.19 (m, 2H), 7.35–7.45 (m, 3H), 6.40 (br s, 1H), 3.70–3.77 (m, 4H), 3.35–3.42 (m, 2H), 2.66–2.71 (m, 2H), 2.47–2.55 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 184 (C), 170.2 (C), 133.3 (C), 129.9 (CH), 128.5 (2CH), 127.9 (2CH), 66.9 ($2CH_2$), 56.2 (CH_2), 53.2 ($2CH_2$), 42.1 (CH_2). IR (neat, ν/cm^{-1}): 3269 (w), 2970 (w), 1739 (s), 1561 (s), 1430 (m), 1349 (s), 1217 (s), 1117 (m), 707 (s). HRMS (ES-TOF$^+$) calculated for $C_{14}H_{19}N_4SO$ 291.1280, found 291.1279.

4.2.6. (Rac)-Methyl 4-methyl-2-((3-phenyl-1,2,4-thiadiazol-5-yl) amino)pentanoate (12)

Yellow oil; yield: 73%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12–8.19 (m, 2H), 7.37–7.44 (m, 3H), 6.15 (d, J = 8.4 Hz, 1H), 4.45–4.50 (m, 1H), 3.79 (s, 3H), 1.70–1.82 (m, 3H), 0.99 (t, J = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 183.0 (C), 173.0 (C), 169.8 (C), 133.1 (C), 129.9 (CH), 128.4 (2CH), 128.0 (2CH), 57.2 (CH), 52.6 (CH_3), 41.8 (CH_2), 24.8 (CH), 22.7 (CH_3), 22.0 (CH_3). IR (neat, ν/cm^{-1}): 3297 (w), 2957 (m), 1744 (s), 1551 (s), 1469 (s), 1433 (s), 1345 (s), 1273 (m), 1205 (s), 1171 (m), 708 (s). HRMS (ES-TOF$^+$) calculated for $C_{15}H_{20}N_3O_2S$ 306.1276, found 306.1276.

4.2.7. 5-(Azetidin-1-yl)-3-phenyl-1,2,4-thiadiazole (13)

Colourless solid; melting range: 103.5–104.3 °C; yield: 84%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15–8.25 (m, 2H), 7.37–7.45 (m, 3H), 4.18 (app t, J = 7.6 Hz, 4 H), 2.50 (app p, J = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 184.3 (C), 170.4 (C), 133.4 (C), 129.8 (CH), 128.4 (2CH), 128.1 (2CH), 53.7 ($2CH_2$), 17.8 (CH_2). IR (neat, ν/cm^{-1}): 3045 (w), 2949 (w), 2870 (w), 1745 (w), 1575 (s), 1463 (s), 1432 (s), 1352 (s), 1283 (m), 702 (s). HRMS (ES-TOF$^+$) calculated for $C_{11}H_{12}N_3S$ 218.0752, found 218.0757. *Crystal data for* ***13***: $C_{11}H_{11}N_3S$, M = 217.29, triclinic, space group P -1, a = 7.3473 (4), b = 12.0606(7), c = 12.6147(7) Å, α = 71.093(5), β = 75.062(5), γ = 81.387(5)°, U = 1019.08(11) Å^3, F(000) = 456, Z = 4, D_c = 1.416 mg m^{-3}, μ = 0.284 mm^{-1} (Mo-Kα, λ = 0.71073 Å), T = 120(1) K. 15847 reflections were collected on an Agilent Xcalibur diffractometer (Sapphire-3 CCD detector, fine-focus tube, graphite monochromator) yielding 5660 unique data (R_{merg} = 0.034). The structure was solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL and OLEX2 software.[29,30] All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were placed into calculated positions and refined in riding mode. Final $wR_2(F^2)$ = 0.1035 for all data 271 refined parameters), conventional R_1 (F) = 0.0383 for 4524 reflections with $I \geqslant 2\sigma$, GOF = 1.021. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1519611.

4.2.8. (Rac)-(2R,4R,5S)-2-Ethyl 4-methyl 4-methyl-1-(3-phenyl-1,2,4-thiadiazol-5-yl)-5-(thiophen-2yl)pyrrolidine-2,4-dicarboxylate (14)

Yellow oil; yield: 79%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15–8.10 (m, 2H), 7.42–7.34 (m, 4H), 7.30 (dd, J = 5.0, 1.2 Hz, 1H), 6.98 (dd, J = 5.1, 3.6 Hz, 1H), 4.84 (s, 1H), 4.74 (dd, J = 10.2, 6.9 Hz, 1H), 4.42–4.28 (m, 2H), 3.45 (s, 3H), 3.08 (dd, J = 13.1, 10.3 Hz, 1H), 2.35 (dd, J = 13.1, 7.0 Hz, 1H), 1.56 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.0 (C), 171.9 (C), 170.8 (C), 169.3 (C), 138.6 (C), 133.2 (C), 128.8 (CH), 128.4 (2CH), 128.1 (CH), 128.0 (2CH), 126.9 (CH), 126.6 (CH), 71.2 (CH), 62.3 (CH), 61.8 (CH_2), 55.2 (C), 52.2 (CH_3), 36.8 (CH_2), 23.4 (CH_3), 14.3 (CH_3). IR (neat, ν/cm^{-1}): 2971 (w), 1739 (s), 1537 (m), 1465 (m), 1434 (m), 1351 (s), 1230 (m), 1204 (m), 1131 (m), 708 (s). HRMS (ES-TOF$^+$) calculated for $C_{22}H_{24}N_3O_4S_2$ 458.1208, found 458.1208.

4.2.9. 5-(4-Methylpiperazin-1-yl)-3-phenyl-1,2,4-thiadiazole (15)

Off-white solid; melting range: 222.1–225.0 °C; yield: 87%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.17–8.21 (m, 2H), 7.38–7.43 (m, 3H), 3.62 (app t, J = 5.2 Hz, 4H), 2.54 (app t, J = 5.2 Hz, 4H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.1 (C), 170.3 (C), 133.5 (C), 129.8 (CH), 128.4 (2CH), 128.0 (2CH), 54.0 ($2CH_2$), 48.8 ($2CH_2$), 46.2 (CH_3). IR (neat, ν/cm^{-1}): 1590 (w), 1523 (s), 1504 (s), 1440 (m), 1368 (s), 1345 (s), 1131 (m), 1028 (m), 743 (s), 702 (m), 683 (s), 644 (m). HRMS (ES-TOF$^+$) calculated for $C_{13}H_{17}N_4S$ 261.1174, found 261.1186.

4.2.10. 3-Phenyl-5-(4-(pyrrolidin-1-yl)piperidin-1-yl)-1,2,4-thiadiazole (16)

Pale yellow oil; yield: 83%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15–8.20 (m, 2H), 7.35–7.43 (m, 3H), 3.96 (br d, J = 12.2 Hz, 2H), 3.24 (ddd, J = 13.1, 11.3, 3.2 Hz, 2H), 2.55–2.70 (m, 4H), 2.30–2.37 (m, 1H), 1.95–2.05 (m, 2H), 1.75–1.85 (m, 4H), 1.66–1.74 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 184.9 (C), 170.3 (C), 133.5 (C), 129.8 (CH), 128.4 (2CH), 128.0 (2CH), 60.7 (CH), 51.3 ($2CH_2$), 47.7 ($2CH_2$), 30.2 ($2CH_2$), 23.3 ($2CH_2$). IR (neat, ν/cm^{-1}): 2957 (m), 2787 (m), 1743 (w), 1556 (s), 1466 (s), 1432 (s), 1356 (s), 1329 (m), 1294 (s), 1150 (m), 1117 (m), 933 (w), 785 (w), 706 (s). HRMS (ES-TOF$^+$) calculated for $C_{17}H_{23}N_4S$ 315.1643, found 315.1647.

4.2.11. 3-Phenyl-5-(4-phenylpiperazin-1-yl)-1,2,4-thiadiazole (17)

Pale yellow solid; melting range: 135.0–135.6 °C. Yield: 85%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.20–8.27 (m, 2H), 7.40–7.47 (m, 3H), 7.29–7.35 (m, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.96 (t, J = 8.4 Hz, 1H), 3.74–3.79 (m, 4H), 3.32–3.36 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.2 (C), 170.4 (C), 150.9 (C), 133.5 (C), 129.9 (CH), 129.4 (2CH), 128.5 (2CH), 128.0 (2CH), 120.9 (CH), 117.0 (2CH), 49.1 ($2CH_2$), 48.8 ($2CH_2$). IR (neat, ν/cm^{-1}): 2822 (w), 1599 (m), 1554 (s), 1502 (m), 1466 (s), 1433 (s), 1355 (s), 1297 (m), 1230 (s), 1028 (m), 944 (m), 759 (m), 707 (s), 692 (m). HRMS (ES-TOF$^+$) calculated for $C_{18}H_{19}N_4S$ 323.1330, found 323.1331.

4.2.12. (1-Methyl-2-((3-phenyl-1,2,4-thiadiazol-5-yl)thio)-1H-imidazol-5-yl)methanol (18)

Colourless oil; yield: 82%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15–8.19 (m, 2H), 7.39–7.45 (m, 3H), 7.10 (s, 1H), 4.62 (s, 2H), 4.35 (br s, 1H), 3.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.1 (C), 172.7 (C), 136.1 (C), 134.5 (C), 132.2 (C), 130.6 (CH), 129.5 (CH), 128.7 (2CH), 128.2 (2CH), 54.4 (CH_2), 31.8 (CH_3). IR (neat, ν/cm^{-1}): 3100–3500 (br), 2932 (w), 2871 (w), 1465 (s), 1436 (s), 1319 (s), 1275 (s), 1112 (m), 1051 (m), 1025 (s), 953 (w), 823 (w), 782 (w), 708 (s), 692 (m). HRMS (ES-TOF$^+$) calculated for $C_{13}H_{13}N_4S_2O$ 305.0531, found 305.0533.

4.2.13. (1-Butyl-2-((3-phenyl-1,2,4-thiadiazol-5-yl)thio)-1H-imidazol-5-yl)methanol (19)

Colourless oil; yield: 76%. ^1H NMR (400 MHz, $CDCl_3$): δ 8.18–8.24 (m, 2H), 7.40–7.51 (m, 3H), 7.13 (s, 1H), 4.65 (s, 2H), 4.09 (app t, J = 7.8 Hz, 2H), 3.63 (br s, 1H), 1.62–1.75 (m, 2H), 1.33 (hex, J = 7.4 Hz, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.1 (C), 172.4 (C), 135.3 (C), 134.9 (C), 132.3 (C), 130.5 (CH), 129.8 (CH), 128.7 (2CH), 128.2 (2CH), 54.6 (CH_2), 45.4 (CH_2), 33.1 (CH_2), 20.0 (CH_2), 13.6 (CH_3). IR (neat, ν/cm^{-1}): 3000–3500 (br), 2959 (m), 2929 (m), 2873 (w), 1467 (s), 1436 (s), 1320 (s), 1276 (s), 1114 (w), 1055 (m), 1027 (m), 786 (w), 709 (s). HRMS (ES-TOF$^+$) calculated for $C_{16}H_{19}N_4S_2O$ 347.1000, found 347.1006.

4.2.14. (1-(2,6-Difluorobenzyl)-2-((3-phenyl-1,2,4-thiadiazol-5-yl) thio)-1H-imidazol-5-yl)methanol (20)

Colourless solid; melting range: 155.5–158.1 °C; yield: 70%. ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.10–8.15 (m, 2H), 7.50–7.55 (m, 3H), 7.32 (tt, J = 8.5, 6.6 Hz, 1H), 7.23 (s, 1H), 7.03 (app t, J = 8.3 Hz, 2H), 5.47 (s, 2H), 5.37 (t, J = 5.4 Hz, 1H), 4.55 (d, J = 5.4 Hz, 2H). ^{13}C NMR (101 MHz, d_6-DMSO): δ 185.4 (C), 171.4 (C), 161.1 (2CF, dd, J = 249, 8 Hz), 137.7 (C), 134.4 (C), 132.2 (C), 131.6 (CH, app t, J = 11 Hz), 131.2 (CH), 129.5 (2CH), 129.1 (CH), 128.1 (2CH), 112.3 (2CH, m), 111.9 (C, app t, J = 18 Hz), 53.8 (CH_2), 37.7 (CH_2). ^{19}F NMR (376 MHz, d_6-DMSO): δ -114. IR (neat, ν/cm^{-1}): 3000–3450 (br), 1628 (w), 1467 (s), 1438 (s), 1424 (m), 1321 (m), 1277 (m), 1236 (m), 1049 (s), 1026 (s), 987 (s), 902 (m), 868 (m), 789 (s), 702 (s). HRMS (ES-TOF$^+$) calculated for $C_{19}H_{15}N_4S_2F_2O$ 417.0655, found 417.0648. *Crystal data for* ***20***: $C_{19}H_{14}N_3S$, M = 416.46, monoclinic, space group P 2_1/c, a = 37.5101(19), b = 7.0468(4), c = 14.0246(7) Å, β = 100.807(2) °, U = 3641.3(3) Å^3, F(000) = 1712, Z = 8, D_c = 1.519 mg m^{-3}, μ = 0.331 mm^{-1} (Mo-Kα, λ = 0.71073 Å), T = 120(1)K. 50,305 reflections were collected on an Bruker D8Venture diffractometer (Photon 100 CMOS detector, IμS-microsource, focusing mirrrors) yielding 8358 unique data (R_{merg} = 0.057). The structure was solved by direct method and refined as a 2-component twin by full-matrix least squares on F^2 for all data using SHELXTL and OLEX2 software.[29,30] H-atoms were placed into calculated positions and refined in riding mode. Final $wR_2(F^2)$ = 0.1919 for all data (487 refined parameters), conventional R_1 (F) = 0.0770 for 7497 reflections with $I \geqslant 2\sigma$, GOF = 1.021. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1519612.

4.2.15. 5-(4-Bromophenoxy)-3-phenyl-1,2,4-thiadiazole (21)

Colourless solid; melting range: 82.3–84.9 °C; yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13–8.22 (m, 2H), 7.60 (d, J = 8.9 Hz, 2H), 7.40–7.48 (m, 3H), 7.30 (d, J = 8.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.6 (C), 169.2 (C), 153.9 (C), 133.3 (2CH), 132.6 (C), 130.6 (CH), 128.6 (2CH), 127.9 (2CH), 121.9 (2CH), 120.1 (C). IR (neat, ν/cm^{-1}): 3060 (w), 1510 (m), 1480 (m), 1455 (m), 1334 (m), 1247 (m), 1189 (m), 1067 (m), 1009 (m), 827 (m), 777 (m), 701 (s), 687 (s). HRMS (ES-TOF$^+$) calculated for $C_{14}H_{10}N_2$-SBrO 332.9697, found 332.9696.

For preparing bromobenzimidamide HCl-salts **22**–**24** the corresponding bromobenzonitriles (10 mmol, 1.0 equiv., 0.8 M, THF) were treated at ambient temperature with a solution of NaHMDS (1.5 M, THF, 1.2 equiv., 8 mL). The resulting reaction mixture was stirred at ambient temperature for 1 h before being quenched by addition of water (5 mL). After addition of aqueous hydrochloric acid (1 M, 15 mL) the aqueous layer was separated and evaporated to about 15% of its original volume resulting in crystallization of the desired HCl-salts **22**–**24** which were isolated in pure form as beige solids after filtration and drying at high vacuum.

4.2.16. 2-Bromobenzimidamide hydrochloride (22)

Beige solid; yield: 77%. ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.70 (s, 2H), 9.64 (s, 2H), 7.79–7.85 (m, 1H), 7.54–7.65 (m, 3H). ^{13}C NMR (101 MHz, d_6-DMSO): δ 166.3 (C), 133.6 (CH), 133.5 (CH), 132.2 (C), 130.0 (CH), 128.4 (CH), 120.1 (C). IR (neat, ν/cm^{-1}): 3216 (br m), 3042 (br s), 1669 (s), 1595 (m), 1454 (m), 1425 (m), 1040 (m), 727 (s), 677 (m). HRMS (ES-TOF$^+$) calculated for $C_7H_8N_2Br$ 198.9871, found 198.9866.

4.2.17. 3-Bromobenzimidamide hydrochloride (23)

Beige solid; yield: 81%. ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.74 (s, 2H), 9.50 (s, 2H), 8.12 (t, J = 1.8 Hz, 1H), 7.88–7.96 (m, 2H), 7.56 (t, J = 8.1 Hz, 1H). ^{13}C NMR (101 MHz, d_6-DMSO): δ 165.0 (C), 136.9 (CH), 131.5 (CH), 131.3 (CH), 130.4 (C), 127.8 (CH), 122.4 (C). IR (neat, ν/cm^{-1}): 3239 (br s), 3027 (br s), 1673 (s), 1519 (s), 1465 (s), 1080 (m), 884 (m), 796 (m), 710 (s), 659 (s). HRMS (ES-TOF$^+$) calculated for $C_7H_8N_2Br$ 198.9871, found 198.9873.

4.2.18. 4-Bromobenzimidamide hydrochloride (24)

Beige solid; yield: 85%. ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.58 (br s, 2H), 9.42 (br s, 2H), 7.85 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H). ^{13}C NMR (101 MHz, d_6-DMSO): δ 165.4 (C), 132.5 (2CH), 130.7 (2CH), 128.1 (C), 127.7 (C). IR (neat, ν/cm^{-1}): 3322 (br s), 3135 9br s), 1669 (s), 1593 (s), 1480 (m), 1428 (m), 1071 (m), 1009 (m), 841 (m), 776 (m), 695 (s), 623 (s). HRMS (ES-TOF$^+$) calculated for $C_7H_8N_2Br$ 198.9871, found 198.9873.

In order to synthesise 5-chloro-1,2,4-thiadiazoles **25**–**27** stock solutions of **5** (0.45 M in EtOAc) and the desired substrates **22**–**24** (0.4 M in water) were prepared and injected into the sample loops of a Vapourtec R-series flow system. Both streams (0.17 mL/min each) were combined in a *T*-piece and subsequently mixed with a stream of aqueous NaOH (1.5 M, 0.33 mL/min) prior to entering two successive tubular flow reactors (10 mL each, rt). Upon exiting the second flow reactor the combined reaction stream passed a back-pressure regulator (75 psi) before being collected into a flask. After aqueous extraction (3 x 10 mL water) the organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The organic residue was further purified by silica column chromatography using EtOAc/hexanes (1/99 to 20/80) as eluent yielding the desired thiadiazoles (**25**–**27**) in pure form after evaporation of all volatiles.

4.2.19. 3-(2-Bromophenyl)-5-chloro-1,2,4-thiadiazole (25)

Yellow oil; yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J = 7.7, 1.8 Hz, 1H), 7.71 (dd, J = 8.0, 1.2 Hz, 1H), 7.41 (td, J = 7.6, 1.3 Hz, 1H), 7.31 (ddd, J = 8.0, 7.4, 1.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8 (C), 171.2 (C), 134.2 (CH), 133.0 (C), 132.3 (CH), 131.4 (CH), 127.4 (CH), 121.9 (C). IR (neat, ν/cm^{-1}): 3058 (w), 1591 (w), 1468 (m), 1451 (s), 1292 (s), 1251 (m), 1060 (s), 1026 (m), 899 (m), 766 (m), 734 (s). HRMS (TOF AP$^+$) calculated for $C_8H_5N_2SBrCl$ 274.9045, found 274.9051.

4.2.20. 3-(3-Bromophenyl)-5-chloro-1,2,4-thiadiazole (26)

Yellow oil; yield: 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (t, J = 1.8 Hz, 1H), 8.14 (dt, J = 7.8, 1.3 Hz, 1H), 7.59 (ddd, J = 7.9, 2.0, 1.1 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4 (C), 170.5 (C), 133.9 (CH), 133.6 (C), 131.1 (CH), 130.3 (CH), 126.6 (CH), 122.9 (C). IR (neat, ν/cm^{-1}): 3069 (w), 1568 (w), 1469 (s), 1458 (s), 1427 (m), 1281 (s), 1057 (s), 907 (m), 792 (m), 726 (s), 677 (s). HRMS (TOF AP$^+$) calculated for $C_8H_5N_2SBrCl$ 274.9045, found 274.9073.

4.2.21. 3-(4-Bromophenyl)-5-chloro-1,2,4-thiadiazole (27)

Off-white amorphous solid; yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3 (C), 171.1 (C), 132.1 (2CH), 130.8 (C), 129.6 (2CH), 125.6 (C). IR (neat, ν/cm^{-1}): 2924 (w), 1715 (w), 1591 (m), 1461 (m), 1397 (m), 1305 (m), 1272 (m), 1109 (m), 1058 (s), 1007 (m), 894 (m), 829 (s), 732 (s). HRMS (TOF AP$^+$) calculated for $C_8H_4N_2SBrCl$ 273.8967, found 273.8989.

Acknowledgement

We gratefully acknowledge financial support by the Royal Society (to MB and IRB) for undertaking this study. We also want to express our gratitude to Dr Andrej Batsanov and Dr Dmitry Yufit (both Department of Chemistry, University of Durham) for solving the single crystal X-ray structures of compounds **13** and **20**.

A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2017.01.022.

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