An efficient one-pot synthesis of 5-(substituted amino)-1,2,4-thia- and -oxa-diazoles

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A general protocol for the synthesis of 5-(substituted amino)-1,2,4-thiadiazoles by the cyclocondensation reaction of amidoximes with *N*-substituted thioureas in the presence of KF/Al_2O_3, and of 5-(cyclohexylamino)-1,2,4-oxadiazoles with DCC in the presence of KF/Al_2O_3 and thiourea, is described. The structures of the new compounds were elucidated by spectroscopic and physical data, and the crystal structure determination by X-ray diffraction of three examples.

Keywords: amidoximes, 1,2,4-thiadiazole, 1,2,4-oxadiazoles, thioureas, KF/Al_2O_3 catalysis

Amidoximes are important precursors of, in particular, O,N,S-containing heterocycles of various sizes, including oxadiazoles and thiadiazoles.[1,2] 1,2,4-Thiadiazoles are an important class of heterocycle, extensively studied because of their biological activities; they have been proposed as fungicides, herbicides, bactericides, and for industrial uses as dyes, lubricant additives, and vulcanisation accelerators. Cephalosporins incorporating a 1,2,4-thiadiazole ring in the side chain have good antibiotic and antimicrobial properties. It is claimed that 1,2,4-thiadiazole-3,5-diamine derivatives are useful in the treatment of hypertension and recently as cathepsin B inhibitors.[3-12]

The unsubstituted 1,2,4-thiadiazole ring was first prepared and characterised in 1955, but products containing this ring system were described as early as 1821. The synthesis of a wide range of 1,2,4-thiadiazoles through a variety of starting compounds has been described in the literature.[13] The formation of 1,2,4-thiadiazoles from amidoximes was first observed by Tiemann, who used isothiocyanates.[14,15] The reaction between amidoximes and sulfenyl amidines with phenyl isothiocyanates has also been used to obtain 5-amino and 3-substituted 1,2,4-thiadiazoles.[16-18] The use of nitriles has been reported for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles.[19,20] The oxidative cyclisation of thioacylamidines was reported for the synthesis of unsymmetrical 3,5-diaryl and 3,5-dialkyl-1,2,4-thiadiazoles.[21-23]

The 1,2,4-oxadiazole[24-26] nucleus is often used as a classical bioisosteric replacement for the amide or ester functionality [27,28] because of its electronic properties. Its derivatives can be found in a vast number of compounds with biological activity, such as ligands of benzodiazepine receptors,[28,29] anti-inflammatory agents,[30-32] antiviral agents,[33] inhibitors of protein tyrosine phosphatases,[34] agonists of muscarinic receptors,[35,36] inhibitors of Src SH2,[37] antagonists of histamine H3 receptors,[38] integrin receptor antagonists,[39] angiotensin II receptor antagonists and HIV-1 reverse transcriptase inhibitors.[40,41] 1,2,4-Oxadiazole moieties have been used in the design of dipeptidomimetics in peptide building blocks.[42]

On account of the interest in the synthesis and uses of heterocycles containing the thiadiazole ring mentioned above, and as part of our research into amidoxime-based heterocycles bearing O,N,S atoms,[43] we have devised a one-pot synthesis of amino-substituted 1,2,4-thiadiazoles. We report here what is, to the best of our knowledge, the first synthesis of 5-anilino-1,2,4-thiadiazoles using amidoximes and *N*-substituted thioureas as starting compounds in the presence of the heterogeneous catalyst potassium fluoride on alumina, and also the formation of 5-cyclohexylamino-1,2,4-oxadiazoles from the amidoximes and DCC (dicyclohexyl carbodiimide) in the presence of a thiourea – KF/Al_2O_3 mixture, one that has been widely used as a heterogeneous catalyst for various organic reactions.[44-48]

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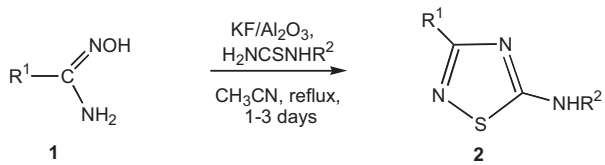
Results and discussion

The reaction between monosubstituted amidoximes **1a-k** which were obtained according to the procedures described in the literature[1,2,43,49-56] and *N*-substituted thioureas in the presence of KF/Al_2O_3 in refluxing acetonitrile within 1-3 days afforded 3-substituted 5-anilino- (*p*-toluidino in the case of **2i** and **2j**) 1,2,4-thiadiazoles **2a–k** (Scheme 1 and Table 1).

Considering the tautomeric and mesomeric structures of amidoximes and thioureas,[57-61] we may propose a reaction mechanism leading to the amino-substituted 1,2,4-thiadiazole ring as shown in Scheme 2.

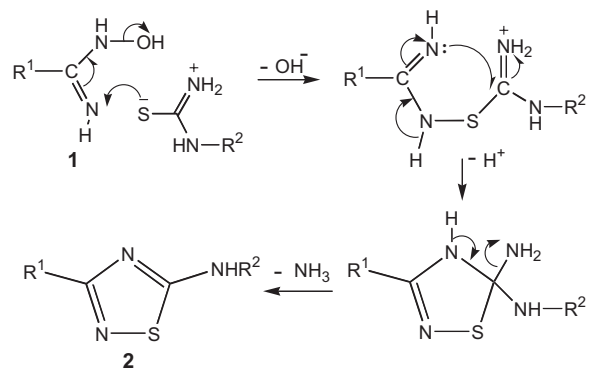


1 2

Scheme 1 3-Aryl-5-arylamino-1,2,4-thiadiazoles.

Table 1 Preparation of 1,2,4-thiadiazoles (Scheme 1)

Compd	R^1	R^2	Time/days	Yield/%
2a	Ph	Ph	3	15
2b	4-$CH_3C_6H_4$	Ph	3	79
2c	4-ClC_6H_4	Ph	3	93
2d	4-BrC_6H_4	Ph	3	43
2e	4-IC_6H_4	Ph	3	43
2f	4-$O_2NC_6H_4$	Ph	1	37
2g	2-thienyl	Ph	3	96
2h	4-pyridyl	Ph	3	47
2i	2-naphthyl	Ph	3	45
2j	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	3	79
2k	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	3	55



1 2

Scheme 2 Proposed mechanism for formation of **2**.

In the first step, the sulfur atom of the *N*-substituted thiourea can attack the imino nitrogen of the amidoxime, in the imino-hydroxylamine tautomer, with concomitant displacement of the hydroxy group from the second nitrogen atom, forming a water molecule. In the second step, the nitrogen lone pair of the new imine group may attack the central carbon of the isothiouronium group, followed by release of ammonia as depicted in Scheme 2, leading to the stable aromatic 1,2,4-thiadiazole ring.

The structures of all the new compounds were determined by spectroscopic and physical data including X-ray measurements on **2a** and **2b** (Figs 1 and 2).

1,2,4-Thiadiazole compounds **2a–k** showed NH stretching absorptions at around 3200–3380 cm^{-1} in the IR spectra. The NH stretching vibration of the *p*-nitrophenyl thiadiazole (**2f**) appeared at the highest value; the lowest one was for that (**2k**) carrying the electron-donating methoxy substituent on the benzene ring at position 3 of the thiadiazole ring.

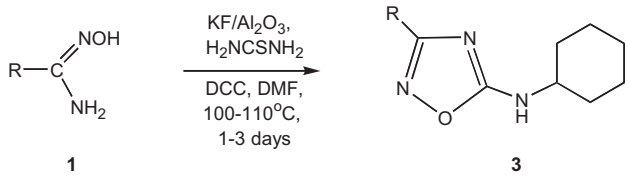
In their ^{1}H NMR spectra, the chemical shifts of the NH protons of compounds **2a–k** appeared at around δ 10-11 ppm when run in DMSO-d_6 and 7.50–8.20 ppm when measured in $CDCl_3$. The ^{13}C chemical shifts of C-3 of the thiadiazole ring appear at low field, varying between 180 and 168 ppm, while those of C-5 resonate at somewhat higher field.

The electron impact mass spectra of the compounds showed fragments which may be attributed to the formation of nitrile sulfide,[62] *N*-substituted thiazirene and phenyl isothiocyanate ions. The relative intensities of these moieties differ according to the nature of the groups R. In order for these fragmentation pathways to be confirmed by exact mass measurements, further work is being considered.

In contrast to the results described above, when the reagents amidoxime **1** and DCC (dicyclohexylcarbodiimide) were heated to *ca* 100ºC in the presence of thiourea and the heterogeneous catalyst mixture KF/Al_2O_3 in DMF as solvent, the major reaction product was found to be the corresponding 3-aryl-5-cyclohexylamino-1,2,4-oxadiazole **3** (Scheme 3 and Table 2).

A reaction mechanism leading to the formation of 5-cyclohexylamino-1,2,4-oxadiazoles **3a–k** may be depicted as in Scheme 4.

The COSY and HETCOR spectra of the cyclohexylamino-1,2,4-oxadiazole **3c** also clearly showed the relationship of the connectivities of NH and CH hydrogens on adjacent carbon of cyclohexane ring and related carbons. An X-ray crystal structure of compound **3a** confirmed the relative dispositions of the substituents and the heteroatoms in the molecule (Fig. 3).



1 3

Scheme 3 3-Aryl-5-cyclohexylamino-1,2,4-oxadiazoles.

Table 2 Preparation of 1,2,4-oxadiazoles (Scheme 3)

Compd	R	Time/days	Yield/%
3a	Ph	2	45
3b	4-$CH_3C_6H_4$	1	86
3c	4-ClC_6H_4	1	98
3d	4-BrC_6H_4	1	72
3e	4-IC_6H_4	2	31
3f	4-$O_2NC_6H_4$	3	72
3g	2-thienyl	3	81
3h	4-pyridyl	3	73
3i	1-naphthyl	2	74
3j	2-naphthyl	2	85
3k	4-$CH_3SC_6H_4$	2	58

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker and Varian spectrometers (200, 300 and 400 MHz for proton and 75 MHz and 100 MHz for carbon). IR spectra were recorded on a Jasco 430 FT/IR and Shimadzu FTIR-8400S instruments (KBr pellet). Mass spectra were run on Agilent GC 6890N MS 5975 instrument. High resolution mass spectra of the compounds were measured on a VG ZabSpec mass spectrometer (Micromass, Manchester, UK) equipped with Opus V3.3X program package. Melting points were determined on a Meltemp apparatus. Flash column chromatography was performed on Silica Gel (Merck, 230–400 Mesh ASTM). TLC was done using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate, *p*-anisaldehyde and iodine were used for visualisation of the TLC spots. Amidoximes were prepared according to literature procedures described previously.[1,2,43]

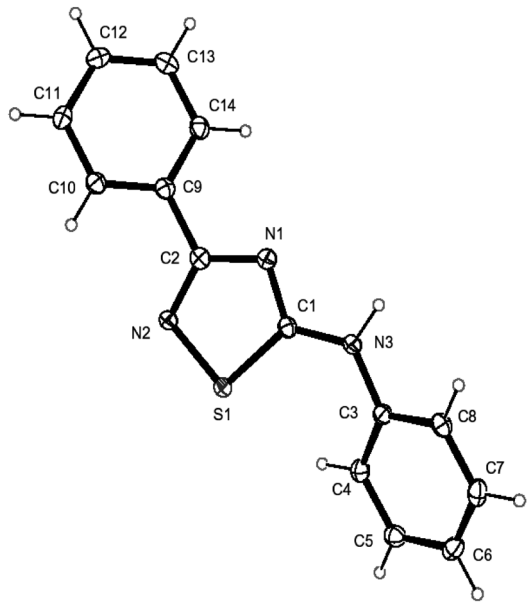


Fig. 1 Structure of 5-anilino-3-phenyl-1,2,4-thiadiazole (**2a**).

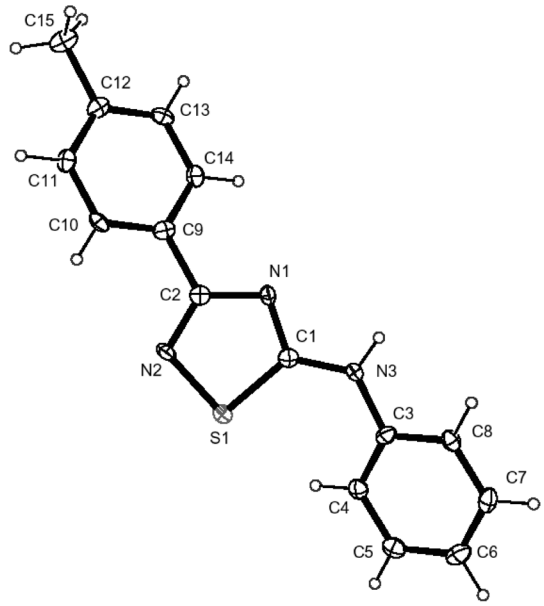


Fig. 2 Structure of 5-anilino-3-(*p*-tolyl)-1,2,4-thiadiazole (**2b**).

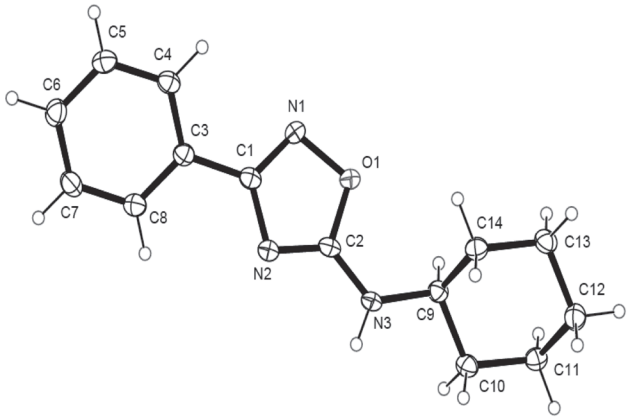


Fig. 3 Structure of 5-cyclohexylamino-3-phenyl-1,2,4-oxadiazole (**3a**).

Preparation of 3-aryl-5-arylamino-1,2,4-thiadiazoles (**2a–k**): *typical procedure*

5-Anilino-3-phenyl-1,2,4-thiadiazole (**2a**): A mixture of benzamidoxime **1a** (3 mmol) and *N*-phenylthiourea (3 mmol) was added to a suspension of Al_2O_3 (2 g) and KF (2 g) in acetonitrile (10 ml). The mixture was heated under reflux with vigorous stirring for 3 days, replenishing the solvent as necessary. The progress of the reaction was monitored by TLC. The reaction mixture was dissolved in acetone and filtered to remove inorganic material. After evaporation of the acetone, the residual crude material was purified by flash column chromatography (n-hexane : ethyl acetate 4 : 1) to give product **2a** (15%) which was recrystallised from benzene as colourless needles, m.p. 177–178°C (lit.[18] 173–174°C). R_f: 0.75 (ethyl acetate: n-hexane 1 : 1).IR: ν_{max} 3230 (N–H), 1603 (C=N), 1564, 1354, 1309 cm^{-1}. NMR ($CDCl_3$): δ_H 8.23 (m, 1H), 7.47 (m, 2H), 7.22(m, 4H); δ_C 181.5, 169.9, 139.3, 133.1, 130.4, 130.1, 128.7, 128.2, 124.5, 118.6. MS (70 eV): *m/z* (%) 253 (92) $[M]^+$, 150 (91), 135 (100), 103 (83), 77 (91), 51 (73).

In a similar manner were prepared:

5-Anilino-3-(4-methylphenyl)-1,2,4-thiadiazole (**2b**): Colourless needles (benzene), m.p. 180–182°C. R_f: 0.67 (ethyl acetate: n-hexane 1 : 2).IR: ν_{max} 3229 (N–H), 1601 (C=N), 1565, 1442, 1461, 1349, 754, 706 cm^{-1}. NMR ($CDCl_3$): δ_H 8.20 (s, 1H), 8.10 (d, J = 8.0 Hz, 2H), 7.43 (t, 2H), 7.28 (t, 3H), 7.18 (t, 1H), 2.42 (s, 3H); δ_C 180.5, 169.5, 140.3, 139.1, 130.3, 130.2, 129.8, 129,2, 127.9, 124.2, 118.3, 21.4. MS (70 eV): *m/z* (%) 267 (51) $[M]^+$, 149 (100), 117 (31), 105 (5), 91 (34), 77 (21), 65 (16), 58 (5), 51 (13). HRMS: calc. for $C_{15}H_{12}N_3S$ 267.0830, found 267.0831.

5-Anilino-3-(4-chlorophenyl)-1,2,4-thiadiazole (**2c**): Colourless needles (benzene), m.p. 187–189°C. R_f: 0.63 (ethyl acetate: n-hexane 1 : 2).IR: ν_{max} 3229 (N–H), 1601 (C=N), 1565, 1349 cm^{-1}. NMR ($CDCl_3$ + DMSO-d_6): δ_H 8.20 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.49–7.12 (m, 5H); δ_C 179.9, 168.2, 140.1, 135.7, 131.9, 129.4, 129.3, 128.7, 123.1, 118.0. MS (70 eV): *m/z* (%) 287 (12) $[M]^+$, 271 (24), 152 (100), 137 (16), 125 (15), 91 (18), 77 (37), 65 (22). HRMS: calc. for $C_{14}H_{10}ClN_3S$ 287.0284, found 287.0282.

5-Anilino-3-(4-bromophenyl)-1,2,4-thiadiazole (**2d**): Light yellow needles (benzene), m.p. 239-241ºC. R_f: 0.69 (ethyl acetate: n-hexane 2 : 1). IR: ν_{max} 3228 (N–H), 1602 (C=N), 1563, 1494, 1440, 1396, 761,701 cm^{-1}. NMR ($CDCl_3$ + DMSO-d_6): δ_H 10.43 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.5 Hz, 4H), 7.30 (t, 2H), 7.01 (t, 1H); δ_C 179.3, 167.3, 140.2, 132.1, 129.9, 129.7, 118.1. MS (70 eV: *m/z* (%) 330 (100) $[M]^+$, 213 (66),183 (24),150 (74), 134 (19), 118 (10), 102 (19), 91 (15), 77 (26), 65 (11), 58 (8), 51 (15). HRMS: calc. for $C_{14}H_{10}BrN_3S_2$ 330.9779, found 330.9782.

5-Anilino-3-(4-iodophenyl)-1,2,4-thiadiazole (**2e**): Light yellow needles (acetone), m.p. 212–213°C. R_f: 0.71 (hexane : ethyl acetate; 2 : 1). IR (KBr): ν = 3288, 3055, 1652, 1560, 1480, 755 cm^{-1}.^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ_H 10.60 (s, 1H, NH), 7.77–7.01 (m, 9H); δ_C 168.4, 137.0, 137.7, 137.4, 129.5, 129.2, 129.0, 128.7, 127.0, 122.9, 117.9, 97.4. MS (70 eV): *m/z* (%) 379 (100) $[M]^+$, 261 (58), 229 (19), 150 (37), 134 (12), 102 (15), 77 (8), 65 (6), 51 (10). HRMS: calc. for $C_{14}H_{10}IN_3S$ 378.9640, found 378.9678.

5-Anilino-3-(4-nitrophenyl)-1,2,4-thiadiazole (**2f**): Colourless needles (benzene–petroleum ether), m.p. 191–193°C. R_f:0.90 (hexane : ethyl acetate 2 : 1) IR: ν_{max} 3380 (N–H), 1646 (C=N), 1587, 1552, 1533 cm^{-1}. NMR ($CDCl_3$ + DMSO-d_6): δ_H 10.86 (d, 1H, NH), 8.26 (m, 5H), 7.57 (m, 2H), 7.32 (m, 2H), 7.02 (s, 1H); δ_C 184.6, 173.6, 171.2, 153.9, 144.8, 142.8, 138.4, 133.9, 133.0, 128.8, 128.0. MS (70 eV): *m/z* (%) 298 (100) $[M]^+$, 268 (9), 180 (27), 150 (78), 134 (13), 118 (24),90 (11), 77 (10), 65 (5), 51 (5). HRMS: calc. for $C_{14}H_{10}N_4O_2S$ 298.0524, found 298.0529.

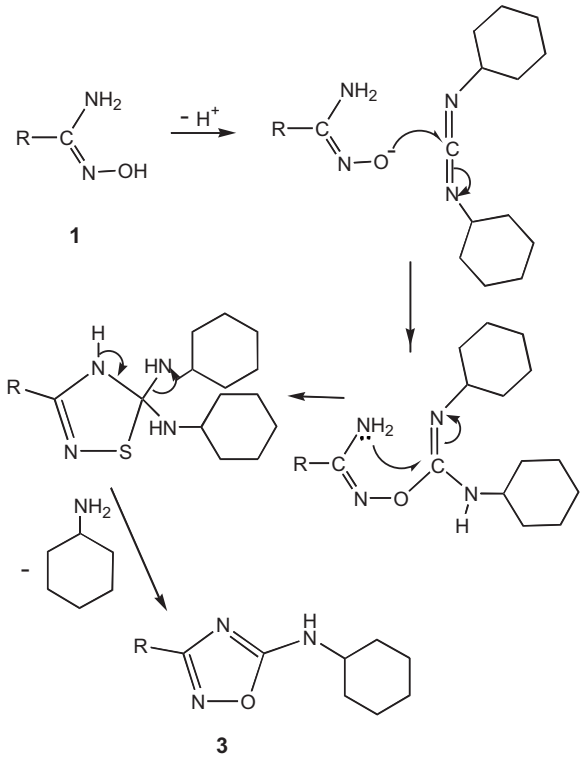
5-Anilino-3-(2-thienyl)-1,2,4-thiadiazole (**2g**): Light yellow needles (benzene), m.p. 134–135°C. R_f: 0.76 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3213 (N–H), 1649 (C=N), 1559, 1489, 1388, 750, 699 cm^{-1}. NMR ($CDCl_3$): δ_H 7.77 (m, 1H), 7.48 (m, 2H), 7.37 (m, 3H), 7.25–7.08 (m, 3H); δ_C 168.0, 136.9, 130.1, 129.7, 129.6, 129.2, 128.8, 128.6, 128.1, 124.4, 118.7. MS (70 eV): *m/z* (%) 259 (100) $[M]^+$, 150 (31),141 (94),109 (22), 77 (8), 65 (4), 51 (4). HRMS: calc. for $C_{12}H_9N_3S_2$ 259.0238, found 259.0237.

5-Anilino-3-(4-pyridyl)-1,2,4-thiadiazole (**2h**): Light orange needles (acetone), m.p. 177–178°C. R_f: 0.36 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3271, 3040, 1644, 1593, 1459, 751 cm^{-1}. NMR ($CDCl_3$ + DMSO-d_6): δ_H 10.44 (s, 1H, NH), 8.39 (s, 2H), 7.56 (s, 2H), 7.23 (m, 2H), 6.98 (m, 2H), 6.71(m, 1H); δ_C 168.8, 166.4, 150.3, 137.9, 135.1, 129.1, 123.2, 121.1, 118.1. MS (APCI,100 eV, positive polarity): *m/z* (%) 255 (82) $[M + H]^+$, 239 (100), 105 (18). HRMS: calc. for $C_{13}H_{10}N_4S$ 254.0626, found 254.0630.

5-Anilino-3-(2-naphthyl)-1,2,4-thiadiazole (**2i**): Light yellow needles (hexane : ethyl acetate 2 : 1), m.p. 173–175°C. R_f: 0.75 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3230, 3136, 3090, 2962, 1600, 1566, 1462, 1442, 752, 488 cm^{-1}. NMR: δ_H (DMSO-d_6) 10.62 (s, 1H, NH), 8.74 (s, 1H), 8.36 (d, J = 8.4 Hz, 1H), 7.97–7.08 (m, 8H) δ_C ($CDCl_3$ + DMSO-d_6) 179.6, 169.2, 140.1, 133.9, 133.0, 132.2, 131.0, 130.7, 129.3, 128.7, 128.1, 127.8, 127.7, 128.1, 127.8, 127.7, 126.9, 126.4, 125.0, 123.0, 117, 9. MS (70 eV): *m/z* (%) 303 (96) $[M]^+$, 185 (100), 153 (79), 127 (19), 77 (10), 65 (3), 51 (5). HRMS: calc. for $C_{18}H_{13}N_3S$ 303.0830, found 303.0842.

5-(4-Methylanilino)-3-(4-methylphenyl)-1,2,4-thiadiazole (**2j**): Light yellow needles (benzene), m.p. 180–182°C. R_f: 0.67 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3228 (NH), 1599 (C=N), 1562, 1347, 1442, 812, 739 cm^{-1}. NMR ($CDCl_3$ + DMSO-d_6): δ_H 10.03 (s, 1H, NH), 8.10 (d, J = 7.6 Hz, 2H), 7.38 (m, 3H), 7.26 (d, J = 7.9 Hz, 2H), 7.18 (d,J = 7.9 Hz, 2H), 2.40 (s, 3H, CH_3), 2.34 (s, 3H, CH_3); δ_C 180.2, 169.5, 140.0, 137.8, 132.9, 130.8, 129.3, 127.9, 118.3, 21.6, 20.9. MS (70 eV): *m/z* (%) 281 (100) $[M]^+$, 164 (76), 149 (100), 131 (21), 117 (42), 105 (9), 91 (48), 77 (21), 65 (15), 51 (6). HRMS: calc. for $C_{16}H_{15}N_3S$ 281.0987, found 281.0995.

3-(4-Methoxyphenyl)-5-(4-methylanilino)-1,2,4-thiadiazole (**2k**): Light yellow needles (benzene), m.p. 138–140°C. R_f: 0.72 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3201, 1608, 1563, 1460, 1345,



Scheme 4 Proposed mechanism for formation of **3**.

1252, 1171, 839, 758 cm^{-1}. NMR ($CDCl_3$ + DMSO-d_6): δ_H 10.15 (s, 1H, NH), 8.18 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 7.9 Hz, 2H), (s, 3.85, 3H, OCH_3), 2.27 (s, 3H, CCH_3); δ_C 180.0, 169.2, 161.0, 137.8, 132.8, 129.9, 129.7, 129.5, 126.4, 118.3, 115.2, 113.8, 55.4, 20.9. MS (70 eV): *m/z* (%) 297 (100) $[M]^+$, 165 (98), 150 (25), 133 (40), 122 (9). HRMS: calc. for $C_{16}H_{15}N_3OS$ 297.0936, found 297.0950.

Preparation of 3-aryl-5-cyclohexylamino-1,2,4-oxadiazoles (**3a-k**): *typical procedure*

5-Cyclohexylamino-3-phenyl-1,2,4-oxadiazole (**3a**): The amidoxime **1a** (1 mmol, 0.136 g), thiourea (1 mmol, 0.076 g), *N*,*N'*-dicyclohexyl carbodiimide (DCC) (2.42 mmol, 0.5 g) and KF + Al_2O_3 (1 : 1 ratio, 1 g) were mixed in DMF (5 ml), and the mixture was stirred and heated at 90–100°C in an oil-bath for about 60 h. After the reaction was complete (monitored by TLC), the DMF was removed under reduced pressure and the remaining yellow crude material was chromatographed on a silica gel column (hexane : ethyl acetate 2 : 1). After the evaporation of solvent, recrystallisation from acetone gave **3a** as colourless needles (45%), m.p. 119–121°C (Lit.[62] 127°C). R_f: 0.70 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3288, 3246, 2937, 2852, 1641, 1389, 1098 cm^{-1}. NMR ($CDCl_3$): δ_H 8.02–7.99 (m, 2H), 7.48–7.43 (m,3H), 5.63 (d, J = 7.7 Hz, 1H, NH), 3.68 (m,1H), 2.10 (m, 2H), 1.75 (m, 2H), 1.62 (m, 1H), 1.46–1.17 (m, 5H); δ_C 170.6, 168.3, 136.1, 130.7, 128.6, 127.2, 52.8, 33.2, 32.8, 25.4, 25.3, 24.6. MS (70 eV): *m/z* (%) 243 (60) $[M]^+$, 200 (12), 174 (19), 161 (90), 145 (40), 140 (32), 119 (100), 103 (35), 97 (29), 77 (47), 55 (34). HRMS: calc. for $C_{14}H_{17}N_3O$ 243.1372, found 243.1368.

In a similar manner were prepared:

5-Cyclohexylamino-3-(4-methylphenyl)-1,2,4-oxadiazole (**3b**): Colourless needles (acetone) (86%), m.p. 138–140°C. R_f: 0.78 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3281, 3255, 2941, 2850, 1644, 1492, 1388, 1101, 826 cm^{-1}. NMR ($CDCl_3$): δ_H 7.86 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 5.34 (d, J = 7.7 Hz, 1H, NH), 3.66 (m, 1H), 2.39 (s, 3H, CH_3), 2.11–1.16 (m, 10 H); δ_C 172.5, 170.4, 142.8, 131.6, 131.5, 131.3, 131.2, 129.3, 129.1, 126.9, 120.3, 54.8, 35.2, 27.3, 26.6, 26.5, 23.4. MS (70 eV): *m/z* (%) 257 (67) $[M]^+$, 214 (9), 188 (14), 175 (100), 159 (22), 140 (21), 133 (66), 117 (27), 97 (18), 91 (33), 55 (19). HRMS: calc. for $C_{15}H_{19}N_3O$ 257.1528, found 257.1525.

3-(4-Chlorophenyl)-5-cyclohexylamino-1,2,4-oxadiazole (**3c**): Colourless needles (acetone) (99%). M.p. 176–178°C. R_f: 0.74 (hexane : ethyl acetate 2 : 1). IR IR: ν_{max} 3286, 3229, 2938, 2854, 1638, 1385, 1098 cm^{-1}. NMR ($CDCl_3$): δ_H 7.92 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.9 Hz, 2H), 5.20 (d, J = 8.0 Hz, 1H, NH), 3.68 (m, 1H), 2.08 (m, 2H), 1.79–1.19 (m, 8H); δ_C 170.8, 167.8, 136.9, 129.1, 128.7, 126.4, 53.1, 33.4, 25.5, 24.7. MS (70 eV): *m/z* (%) 277 (63) $[M]^+$, 234 (13), 208 (18), 195 (99), 179 (38), 153 (100), 137 (43), 111 (30), 97 (37), 83 (19), 55 (49). HRMS: calc. for $C_{14}H_{16}ClN_3O$ 277.0982, found 277.0983.

3-(4-Bromophenyl)-5-cyclohexylamino-1,2,4-oxadiazole (**3d**): Colourless needles (acetone) (72%), m.p. 186–187°C. R_f: 0.6 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3289, 3227, 2933, 2852, 1638, 1410, 832, 759 cm^{-1}. NMR ($CDCl_3$): δ_H 7.85 (d, J = 6.4 Hz, 2H), 7.55 (d, J = 7.6 Hz, 2H), 5.22 (d, J = 7.9 Hz, 1H, NH), 3.66 (m, 1H), 2.09–1.17 (m, 10H); δ_C 170.7, 167.9, 132.0, 128.9, 126.8, 125.4, 53.1, 33.4, 25.5, 24.8. MS (70 eV): *m/z* (%) 321 (63) $[M]^+$, 278 (13), 252 (18), 239 (100), 225 (36), 197 (96), 183 (41), 155 (21), 140 (71), 97 (55), 83 (29), 55 (67). Anal Calcd for $C_{14}H_{16}BrN_3O.0{\cdot}25\ H_2O$: C, 51.65; H, 5.10; N, 12.90; found C, 51.61; H, 5.48; N, 12.53%.

5-Cyclohexylamino-3-(4-iodophenyl)-1,2,4-oxadiazole (**3e**): Colourless needles (acetone) (31%), m.p. 147–149°C. R_f: 0.76 (hexane : ethylacetate2 : 1). IR:ν_{max}3286,3237,2933,2852,1638,1406, 1096, 1007, 969, 831, 759 cm^{-1}. NMR ($CDCl_3$): δ_H 7.78 (d, J = 7.9 Hz, 2H), 7.69 (d, J = 7.6 Hz, 2H), 5.26 (d, J = 7.9 Hz, 1H, NH), 3.66 (m, 1H), 2.17–1.16 (m, 10H); δ_C 170.7, 168.05, 138.0, 129.0, 127.4, 97.5, 53.1, 33.4, 25.5, 24.8. MS: *m/z* (%) 369 (76) $[M]^+$, 287 (100), 271 (27), 245 (65), 229 (32), 140 (32), 102 (27), 83 (13), 55 (29). HRMS: calc. for $C_{14}H_{16}IN_3O$ 369.0338, found 369.0339.

5-Cyclohexylamino-3-(4-nitrophenyl)-1,2,4-oxadiazole (**3f**): Colourless needles (acetone) (72%), m.p. 205–206°C. R_f: 0.69 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3296, 3260, 2942, 2853, 1638, 1532, 1416, 1345, 1091, 862, 748 cm^{-1}. NMR ($CDCl_3$): δ_H 8.32 (d, J = 8.9 Hz, 2H), 8.20 (d, J = 8.9 Hz, 2H), 5.02 (d, J = 7.8 Hz, 1H, NH), 3.70 (m, 1H), 2.12 (m, 2H), 1.75–1.14 (m, 10H); δ_C 170.8, 166.8, 149.1, 133.7, 128.1, 123.8, 53.1, 40.3, 33.1, 25.2, 24.5. MS (70 eV): *m/z* (%) 288 (42) $[M]^+$, 245 (22), 207 (100), 190 (63),164 (91), 140 (48), 97 (39), 83 (29), 67 (31), 55 (68). HRMS: calc. for $C_{14}H_{16}N_4O_3$ 288.1222, found 288.1223.

5-Cyclohexylamino-3-(2-thienyl)-1,2,4-oxadiazole (**3g**): Colourless needles (acetone) (81%), m.p. 124–126°C. R_f: 0.72 ((hexane : ethyl acetate 2 : 1). IR: ν_{max} 3284, 3228, 2928, 2851, 1641, 1554, 1508, 1448, 1432, 1389, 1311, 1009, 852, 706 cm^{-1}. NMR ($CDCl_3$): δ_H 7.68 (d, J = 1.1 Hz, 1H), 7.42 (d, J = 1.2 Hz, 1H), 7.10 (t, 1H), 5.31 (d, J = 7.9 Hz, 1H, NH), 3.65 (m, 1H), 2.09–1.15 (m, 10H); δ_C 172.3, 166.5, 131.3, 130.7, 130.4, 129.5, 54.8, 35.1, 34.8, 27.3, 26.6, 26.5. MS (70 eV): *m/z* (%) 249 (77) $[M]^+$, 167 (100), 151 (18), 125 (50), 109 (24), 97 (24), 83 (9), 55 (23). HRMS: calc. for $C_{12}H_{15}N_3OS$ 249.0936, found 249.0952.

5-Cyclohexylamino-3-(4-pyridyl)-1,2,4-oxadiazole (**3h**): Colourless needles (acetone) (73%), m.p. 124–125°C. R_f: 0.82 ((hexane : ethyl acetate 1 : 2). IR: ν_{max} 3327, 3215, 3152, 2925, 2849, 1638, 1519, 1424, 1393, 1111, 759, 688 cm^{-1}. NMR ($CDCl_3$): δ_H 8.76 (br s, 2H), 7.89 (s, 2H), 5.99 (d, J = 7.1 Hz, 1H, NH), 2.14–1.08 (m, 10 H); δ_C 171.1, 166.7, 150.0, 135.5, 129.3, 121.3, 118.4, 53.0, 49.0, 33.9, 33.1, 30.8, 25.5, 25.3, 24.9, 24.6. MS: *m/z* (%) 244 (48) $[M]^+$, 201 (18), 175 (22), 163 (100), 146 (50), 140 (36), 120 (67), 97 (27), 83 (18), 78 (36), 67 (17), 55 (43). HRMS: calc. for $C_{13}H_{16}N_4O$ 244.1324, found 244.1325.

5-Cyclohexylamino-3-(1-naphthyl)-1,2,4-oxadiazole (**3i**): Light yellow needles (hexane : ethyl acetate 3 : 1) (74%), m.p. 176–176.5°C. R_f: 0.75 ((hexane : ethyl acetate 3 : 1). IR: ν_{max} 3292, 3200, 2931, 2854, 1649, 1535, 1417, 1369, 1259, 1062, 779 cm^{-1}. NMR ($CDCl_3$): δ_H 8.58 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.1 Hz, 1H), 7.75 (d, J = 7.1 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.49–7.23 (m, 3H), 5.40 (d, J = 6.4 Hz, 1H, NH), 3.46 (m, 1H), 1.86 (m, 2H), 1.54–1.37 (m, 3H), 1.21–0.74 (m, 5H); δ_C 170.9, 169.9, 133.8, 131.2, 130.8, 128.7, 128.4, 127.2, 126.37, 126.1, 125.0, 124.8, 52.9, 33.1, 25.2, 24.6. MS (70 eV): *m/z* (%) 293 (35) $[M]^+$, 211 (26), 168 (100), 153 (46), 140 (23), 55 (22), 41 (21). HRMS: Calcd for $C_{18}H_{19}N_3O$ 293.1528; found 293.1535.

5-Cyclohexylamino-3-(2-naphthyl)-1,2,4-oxadiazole (**3j**): Colourless needles (hexane : ethyl acetate 3 : 1) (94%), m.p. 147–148°C. R_f: 0.70 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3292, 3250, 2929, 2852, 1639, 1514, 1467, 1398, 1122, 765 cm^{-1}. NMR ($CDCl_3$): δ_H 8.54 (s, 1H), 8.10 (dd, J = 8.5 1.5 Hz, 1H), 8.03–7.79 (m, 3H), 7.58–7.51 (m, 2H), 5.52 (d, J = 7.5 Hz, 1H),3.79 (m, 1H), 2.16–0.90 (m, 11H) δ_C 170.5, 168.4, 134.5, 133.0, 128.7, 128.4, 127.8, 127.2, 126.5, 124.9, 123.8, 52.9, 33.2, 25.3, 24.6. MS (70 eV): *m/z* (%) 293 (76) $[M]^+$, 211 (100), 168 (88), 153 (91), 140 (35), 127 (56), 97 (21), 55 (41), 41 (32). Anal. Calcd for $C_{18}H_{19}N_3O.0{\cdot}25\ H_2O$: C, 72.63; H, 6.60; N, 14.11; found C, 72.40; H, 6.78; N, 13.98%.

5-Cyclohexylamino-3-(4-methylthiophenyl)-1,2,4-oxadiazole (**3k**): Colourless needles (hexane : ethyl acetate 2 : 1) (80%), m.p. 128–129°C. R_f: 0.78 (hexane : ethyl acetate 2 : 1). IR: ν_{max} 3288, 3238, 2928, 2856, 1643, 1600, 1410, 1384, 1101, 763 cm^{-1}. NMR ($CDCl_3$): δ_H 7.65 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 5.15 (d, J = 7.7 Hz, 1H, NH), 3.43 (m, 1H), 2.28 (s, 3H), 1.86–0.95 (m, 10 H); δ_C 170.4, 168.0, 142.1, 127.5, 125.7, 124.0, 52.8, 33.2, 25.3, 24.6, 15.1. MS (70 eV): *m/z* (%) 289 (10) $[M]^+$, 207 (87), 164 (62), 149 (99), 55 (44), 41 (33). HRMS: Calcd for $C_{15}H_{19}N_3OS$ 289.1249, found 289.1255.

Supplementary data

Crystallographic data of the compounds **2a**, **2c** and **3a** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC Durust32, Durust32CIF, MY69, AA21 and AA1. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: + 44 1223 336033] or by e-mail: deposit@ccdc.cam.ac.uk.

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