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Solid state synthesis of 5–anilino–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazoles

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Abstract

We wish to report the synthesis of 5–anilino–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazoles by a solid state, mechanochemical oxidative cyclization of 3,5–dimethyl–1–[N–(N'–arylthiocarbamoyl) amidino] pyrazoles, which in turn have also been accessed through a solvent free, green technique.

Keywords: 1,2,4–thiadiazole, mechanochemistry, hetarylthiocarbamoylamidine, oxidative cyclization, NMR analysis

1. INTRODUCTION

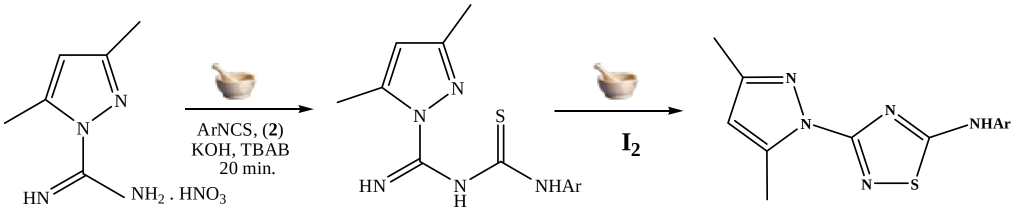
The synthesis of 1,2,4–thiadiazoles, a versatile class of S–N heterocycles, has claimed recent attention owing to their remarkable biological activities since a wide spectrum of therapeutic applications have been reported for substituted 1,2,4–thiadiazoles [1]. The clinically prescribed antibiotic cefozopram is a 1,2,4–thiadiazole derivative. Several reports exist on the pharmacophore properties of 1,2,4–thiadiazoles. For example, 3,5–bis(indolyl)–1,2,4–thiadiazole derivative showed potent cytotoxicity against human cancer cell lines [2] and a substituted 1,2,4–thiadiazole has been identified for the treatment of multiple sclerosis and rheumatoid arthritis [3]. The bioactive properties of 1,2,4–thiadiazole have also received recent attention in G protein coupled receptor modulation [4] and glycogen synthase kinase inhibition [5]. Literature also exists on the antimicrobial, anti–inflammatory, anticancer, anticonvulsant, antidepressant, antioxidant, radio protective, and anti–leishmanial activities of 1,2,4–thiadiazoles [6-8]

Mechanochemical reactions are effected by either hand grinding or by mechanical milling in the absence of solvents [9]. The latter is carried out using using steel balls in a mixer, shaker or planetary mill. Mechanochemical synthesis has been suggested to be advantageous over the conventional solution phase thermal synthesis due to its energy efficiency, product selectivity, operational simplicity, health and environmental safety. This field of synthesis has attracted much recent attention as it also aims to establish safe alternatives to synthesis using solvents. The application of mechanochemical method to a wide variety of organic reactions have recently been reviewed [10]. These reactions include Michael additions, Knoevanagel and Barbier reactions, pinacol rearrangement, Grignard reactions, Wittig and Horner–Wadsworth–Emmons reactions as typical examples. A number of metal–catalyzed transformations, including Suzuki, Heck–Mizoroki, Sonogashira and Glaser couplings, have been done mechanochemically, [11]. Mechanochemistry sometimes becomes the preferred method for reactions that are low–yielding and tedious to conduct in solution. For example, N–heteroacenes are mechanochemically synthesised by cyclocondensation between 1,2–dicarbonyl compounds and 1,2–diaminoarenes, avoiding the formation of side products seen in the corresponding solution phase synthesis [12].

Oxidation of thiourea derivatives to form substituted ureas, formamidinium disulfide and 2–aminothiazoles and 1,2,4–thiadiazoles has been recently reviewed [13]. Oxidative cyclisation of suitable thiocarbamoylamidines, thiocarbamoylguanidines and thioureas resulted in 1,2,4–thiadiazoles [1,15]. A recent, green version of this approach the involved iodine–catalyzed oxidative dimerization of thioamides in water using molecular oxygen as an oxidant [15]. We have earlier reported that 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles are useful starting materials for 5–acyl–2,4–diaminothiazole and 3,5–diamino–1,2,4–triazole synthesis [16]. We now wish to report the synthesis of 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles and their oxidation leading to 5–anilino–1,2,4–thiadiazoles under solid state conditions mechanochemically.

2. RESULTS AND DISCUSSION

We had reported the synthesis of 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles earlier by the reaction of 3,5–dimethylpyrazol–1–ylamidine (**1**), either as a salt, or as its free base, with isothiocyantes **(2)** under thermal condition in presence of solvents [16]. Now we report the application of mechanochemistry for the preparation of hitherto unreported 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles (**3a–e**). The reaction methodology involves a simple hand grinding of reactants; 1–amidino–3,5–dimethylpyrazole nitrate and aryl isothiocyanates in an agate mortar with a pestle for 20 min in presence of solid KOH and tetra–n–butylammonium bromide TBAB as a solid phase transfer catalyst (Scheme 1).



1

3a-e

4a-e

3a :Ar= 3-$CH_3OC_{6-}H_5$
3b :Ar= 3-$CH_3C_{6-}H_5$
3c : Ar= 3-$ClC_{6-}H_5$
3d : Ar= 4-FC_6H_5
3e : Ar= 4-BrC_6H_5

4a :Ar= 3-$CH_3OC_{6-}H_5$
4b :Ar= 3-$CH_3C_{6-}H_5$
4c : Ar= 3-$ClC_{6-}H_5$
4d : Ar= 4-FC_6H_5
4e : Ar= 4-BrC_6H_5

Scheme 1:

The compounds prepared by this mechanochemical approach are found to be identical with those obtained by corresponding, but lengthy, solution phase thermal reaction by TLC analysis, melting point and FTIR spectral data. The newly obtained 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles were characterised by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS. The IR spectrum of the product 3**a** obtained by the reaction of 3,5–dimethylpyrazol–1–ylamidine (**1**) with 3–methoxyphenyl isothiocyanate showed N–H stretching vibrations at 3385 and 3242 cm^{-1}. Bands due to C–H stretching of the aromatic ring appeared at 3055 $cm^{-1.}$ Bands due to C=C bending of aromatic ring were observed at 1633 cm^{-1}. The NMR spectrum of **3a**, recorded in $CDCl_3$ first seemed to indicate the formation of a mixture of products since discreet peaks with well defined integral hydrogen counts were not present in the spectrum. Instead, peaks were generally broad and showed non– integral hydrogen counts. For example, the peak due to the H4 of the pyrazole ring appeared as a cluster of two broad peaks centered at δ5.87 and δ 6.01 respectively. It was then observed that normalisation of peak areas of other peak clusters, based on the combined integrated area under the above cluster of two broad peaks representing H4, indicated that the cluster of three peaks in the region δ1.90–2.80, with peak–centres at δ 1.99, 2.22 and 2.70, accounted for the six hydrogens of the two methyl groups. Similarly, the broad peak centered at δ 3.78 accounted for three hydrogens of the methoxy group and the peak clusters in the region δ 6.70–7.70 accounted for four aryl hydrogens. The three NH hydrogens appeared as a broad peak at δ 7.89, a cluster of two broad peaks in the region δ 8.30–8.80 and another cluster of two peaks in the region δ 10.40–11.30 three NH hydrogens respectively. The ^{13}CNMR spectrum showed peaks at δ 55.40 corresponding to the methoxy carbon, and benzene ring carbons and the pyrazole ring carbons in the region δ 109–160. The reason for the above peak heterogenity and broadening in the NMR spectra in $CDCl_3$ is attributable to the presence of tautomers. The other possibilities of the formation of a mixture of products, or due to product decomposition or dimerisation, were ruled out by the following observations. The repetition of the reaction under entirely different conditions developed earlier by us [16] afforded the same product as evidenced by FTIR, mp and mixed mp studies and in comparable yield, thus excluding the formation of a product mixture. The HRMS data showed no evidence for any other side products. Based on the above data, the structure of the compound obtained from 3,5–dimethylpyrazol–1–ylamidine (**1**) with 3–methoxyphenyl isothiocyanate was assigned as 1–[N–(N'–3–methoxyphenylthiocarbamoyl) amidino]–3,5–dimethylpyrazole **(3a)**. Additional confirmation of the product homogenity of **3a** arose from its subsequent oxidative cyclisation under very mild conditions leading to a single product, as described below. Similar reaction of 3,5–dimethylpyrazol–1–ylamidine nitrate (**1**) with 3–methylphenyl, 3–chlorophenyl, 4–bromophenyl and 4–fluorophenyl isothiocyanates (**2b–e)** afforded 1–[N–(N'–arylthiocarbamoyl)amidino]– 3,5–dimethylpyrazoles **(3b–e)** in fairly good yield.

In the light of our earlier success in the synthesis of heterocycles including 2,4–diaminothiazoles and 1,2,4–triazoles starting from 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles [16] [Jenardanan *et al.,* 1997] and recently reported mechanochemical heterocycle synthesis [Sherin *et al.*, 2015], we have now attempted a solid state synthesis of 5–anilino–3–pyrazol–1–yl–1,2,4–thiadiazoles by the oxidative cyclisation of 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles. Such pyrazole substituted 1,2,4–thiadiazoles had been synthesised by Godfrey and Kurzer by the reaction of acetylacetone on –anilino–3–hydrazino–1,2,4–thiadiazole [17]. Our solid state synthesis of thiadiazoles involved the grinding of 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles (**3a–e**) with iodine for 5–10 mins. The resulting compounds are found to be identical with that obtained from corresponding solution phase reaction. Thus, our work now provides a rapid, solventless alternative to access the title compounds. The IR spectrum of the product **4a** formed by the oxidative cyclisation of 1–[N–(N'–3–methoxyphenylthiocarbamoyl)amidino]–3,5–dimethylpyrazole showed N–H stretching vibrations at 3267 and 3216 cm^{-1}. Bands due to C–H stretching of the aromatic ring appeared at 3066 $cm^{-1.}$ Bands due to C=C stretching of aromatic ring were observed at 1628 cm^{-1}. In the ^{1}H NMR spectrum, two methyl groups in the pyrazole ring were appeared as singlet each at δ 2.19 and 2.56. A singlet at δ 3.78 is assignable to the methoxyphenyl group and another one at δ 6.12 is attributed to the H4 of the pyrazole ring. The four aryl hydrogens appeared as two doublets at δ 6.70 and 7.05, a singlet at δ 7.23 and a triplet at δ 7.33. A singlet at δ 11.19 is ascribed to the NH hydrogen. In the ^{13} C NMR spectrum peaks at 13.82 and 14.10 corresponds to methyl carbons, methoxy carbon appeared at 55.61. The pyrazole, benzene and thiadiazole carbons were seen between 104–180 ppm. The spectral evidences confirm the structure of the compound obtained as 5–(3–methoxyanilino)–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazoles (**4a**).

Table 1: Yield and melting point of 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles (**3a–e**)

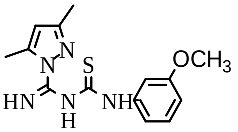
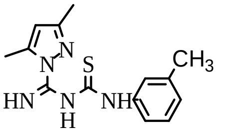
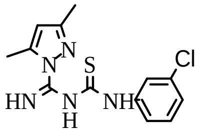
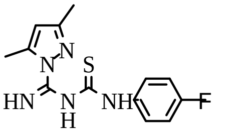
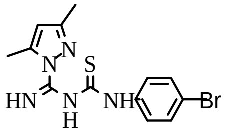
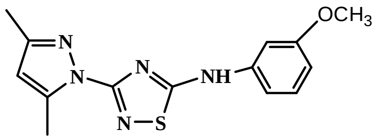
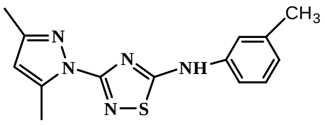
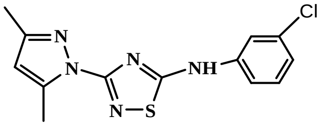
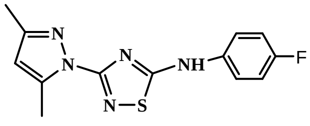
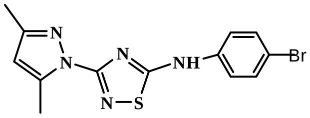
Sl. No.	Compound	Yield (%)	Melting point (°C)
1	 **3a**	65%	115–117
2	 **3b**	63%	86–88
3	 **3c**	75%	136–138
4	 **3d**	60%	121–122
5	 **3e**	62%	123–125

Table 2: Yield and melting point of 5–anilino–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazoles (**4a–e**)

Sl. No.	Compound	Yield (%)	Melting point (°C)
1	 **4a**	68%	225–27
2	 **4b**	64%	240–242
3	 **4c**	63%	275–276

4	 **4d**	68%	253–254
5	 **4e**	62%	222–223

3. EXPERIMENTAL

All melting points are uncorrected and were determined by open capillary method. The thin layer chromatography analyses were performed using silica gel–G. coated on glass plates or commercial plastic plates. The spots were visualized in iodine vapour or under UV light. The IR spectra were recorded on Shimadzu FTIR spectrophotometer. The NMR spectra were recorded in CDCl$_3$ and DMSO on Bruker DPX 400 MHZ NMR spectrometer at room temperature. The HRMS–ESI analysis was performed on an Agilent 6520 QTOF–MS/MS system. All chemicals used were from Sigma Aldrich and E. Merck, India.

3.1. *Synthesis of 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles (3a–e)*

Method A:

1–Amidino–3,5–dimethyl–pyrazole nitrate (100 mg, 0.5 mmol), powdered potassium hydroxide (28 mg, 0.5 mmol) and tetra–n–butylammonium bromide TBAB (5 mg) were ground in a mortar and pestle for 3 min. To this mixture, aryl isothiocyante (0.5 mmol) was added and the grinding continued at room temperature for 15–20 minutes. An initially observed oil like appearance of the ground mixture turned to a solid mass. The solid then was worked up by grinding with petroleum ether, followed by water, to obtain 1–[N–(N'–arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles. The products were then collected by decantation and filtration. Purification involved crystallization from ethanol–water (1:1).

Method B:

The above reactions between 1–amidino–3,5–dimethyl–pyrazole nitrate (**1**) and aryl isothiocyanates (**2a**–e) were repeated under conditions developed earlier in our laboratory. Thus, to a suspension of **1** (100 mg, 0.5 mmol mmol) in N,N–dimethylformamaide (DMF, 2 mL), containing powdered KOH (28 mg, 0.5 mmol), aryl isothiocyanates (0.5 mmol) in DMF (1 mL)was added dropwise with stirring at 0 ^{o}C during 20 mins. The temperature of the reaction mixture was then raised to 65–70 ^{o}C and the stirring was continued for another 2 h. The reaction mixture was then poured into ice water to obtain solid product.

The compounds prepared by this method were:

1–[N–(N'–3–Methoxyphenylthiocarbamoyl)amidino]–3,5–dimethylpyrazole (3a): Yield: Method A: 65%, m.p. 115–117 °C.; Method B: 71%; m. p. 118 °C; IR: 3385, 3242, 3055, 1633, 1539, 1390, 1317, 1114, 968, 825, 684 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, 25 ^{o}C): δ : 1.90–2.80, bm, 6H; 3.70–3.90, b, 3H; 5.80–6.10, b, 1H; 6.40–7.60, m, 4H; 7.70–8.00, b, 1H; 8.30–8.80, b 1H; 10,45–11.25, b,1H ; ^{13}C NMR (100MHz, CDCl$_3$, 25 ^{o}C): δ = 14.13, 14.98, 16.16, 55.40, 111.43, 111.89, 117.85, 129.44, 139.41, 143.96, 151.69, 155.68, 188.64.
HRMS (ESI): [M+H]$^{+}$ 304. 1154 (calcd), 304.1226 (found)

1–[N–(N’–3–methylphenylthiocarbamoyl)amidino]–3,5–dimethylpyrazole (3b): Yield: Method A: 63%, m.p**.** 86–88 ^{o}C. Method B: 70 %; m. p. 87 ^{o}C ; IR: 3194, 3034, 1641, 1481, 1392, 1313, 1124, 975, 840, 775, 684 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, 25 ^{o}C): δ : 1.85–2.80, bm, 9H; 5.75–6.10, b, 1H; 6.90–7.55, m, 4H; 7.80–8.10, b, 1H; 8.35–8.55, b 1H, 10.40–11.15, b,1H.
^{13}C NMR (100MHz, CDCl$_3$, 25 °C): δ = 14.13, 14.90, 14.23, 21.26, 111.33, 115.63, 119.47, 122.62, 12515, 125.44, 126.19, 128.56, 138.63143.95, 151.63, 155.61, 188.62.
HRMS (ESI): [M+H]$^{+}$ 288. 1205 (calcd), 288.1275 (found).

1–[N–(N’–3–Chlorophenylthiocarbamoyl)amidino]–3,5–dimethylpyrazole (3c): Yield: Method A: 75%, m.p. . 136–138 ^{o}C. Method B: 79 %; m. p. 137 ^{o}C ; IR : 3401, 3174, 3058, 1613, 1523, 1479, 1363, 1013, 911 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, 25 ^{o}C): δ : 1.90–2.85, bm, 6H; 5.80–6.15, b, 1H; 7.05–7.55, m, 4H; 7.85–8.20, b, 1H, 8.25–8.60, b 1H, 10.60 –11.20, b,1H.; ^{13}C NMR (100MHz, CDCl$_3$, 25 ^{o}C): δ = 13.66, 13.71, 15.10, 111.63, 116.59, 118.61, 122.47. 122.96, 124.22125.71, 129.73, 130.65, 134.22, 139.39, 143.82, 151.94, 156.16, 188.65; HRMS (ESI): [M+H]$^{+}$ 308. 0658 (calcd), 308.0723 (found).

1–[N–(N’–4–Fluorophenylthiocarbamoyl)amidino]–3,5–dimethylpyrazole (3d): Yield: Method A: 60%, m.p**.** 121–122 °C. Method B: 65 %; m. p. 122 ^{o}C ; IR : 3453, 3200, 3032, 1635, 1501, 1326, 1214, 964, 823 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ : 1.85–2.75, bm, 6H; 5.75–6.15, b, 1H; 6.95–7.65, m, 4H; 7.80–8.05, b, 1H, 8.15–8.90, b 1H, 10.65 –11.25, b,1H ; ^{13}C NMR (100MHz, CDCl$_3$, 25 °C): δ = 13.70, 14.88, 16.19, 111.48, 115.50, 115.72, 126.88, 127.76, 127.84, 134.52, 143.85, 151.81, 155, 88, 162.23, 189.18.
HRMS (ESI): [M+H]$^{+}$ 292. 0954 (calcd), 292.1031 (found).

1–[N–(N’–4–Bromophenylthiocarbamoyl)amidino]–3,5–dimethylpyrazole (3e): Yield: Method A: 62%, m.p**.** 123–125 °C. Method B: 68 %; m. p. 122 ^{o}C; IR : 3408, 3360, 3061, 1620, 1579, 1428, 1285, 1114, 968 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, 25 ^{o}C): δ : 1.80–2.85, bm, 6H; 5.80–6.10, b, 1H; 7.05–7.65, m, 4H; 7.80–8.15, b, 1H, 8.15–8.90, b 1H, 10.45 –11.30, b,1H ; ^{13}C NMR (100MHz, CDCl$_3$, 25 °C): δ = 13.71, 15.10, 16.06, 111.65, 119.34, 125.96, 126.95, 132.00, 137.34, 143.79, 144.79, 151.49, 155,94, 188.67.
HRMS (ESI): [M+H]$^{+}$ 352. 0153 (calcd), 352.0206 (found).

3.2. *Synthesis of 5–anilino–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazoles*

Method A: solid stae reaction

1–[N–(N’–Arylthiocarbamoyl)amidino]–3,5–dimethylpyrazoles (**3a–e**) (0.5 mmol) and iodine (0.5 mmole) were ground for 5–10 mins in an agate mortar. Work up by grinding with few drops dilute aq. ammonia solution, followed by water, afforded solid 5–anilino–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazoles (**4a–e**). The products could be collected by filtration. Purification involved crystallization from ethanol.

Method B:Solution phase reaction

To a solution of **3a–e** (0.5 mmol) in methanol (5mL), iodine solution in methanol (0.5mmol) was added and kept closed at room temperature with occasional shaking for 1 h. Work up with dilute aq. ammonia solution, followed by water, afforded solid 5–anilino–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazoles (**4a–e**). The compounds prepared by the above two methods were identical as shown by TLC, FTIR, m.p. and mixed m. p. anaylsis.

5–(3–Methoxyanilino)–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazole (**4a**): Yield: Method A: 68%, m.p**.** 225–27 °C. Method B: 64%; m. p. 226 ^{o}C ; IR: 3267, 3216, 3066, 1628, 1531, 1463, 1378, 1218, 842, 771 cm^{-1} ; ^{1}H NMR (400 MHz, DMSO, 25 °C): δ = 2.19 (s, 3H, CH$_3$), 2.56 (s, 3H, CH$_3$), 3.78 (s, 3H, OCH$_3$), 6.12 (s, 1H, pyrazole H), 6.70 (d, 1H, ArH, J= 9.2 Hz), 7.05 (d, 1H, ArH, J=7.8 Hz), 7.23 (s, 1H, ArH), 7.33 (t, 3H, ArH, J= 8.2 Hz), 11.19 (s, 1H, NH) ; ^{13}C NMR (100MHz, DMSO, 25 °C): δ = 13.82, 14.10, 55.61, 104.37, 109.05, 109.12, 110.68, 130.80, 140.94, 141.91, 149.90, 158.94, 160.55, 179.12

5–(3–Methylanilino)–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazole (**4b**): yield: Method A: 64%, m.p. 240–42 °C. Method B: 65%; m. p. 240–42 °C ; IR: 3252, 3204, 3081, 1620, 1531, 1382, 1166, 931 cm^{-1} ; ^1H NMR (400 MHz, DMSO, 25 °C): δ = 2.19 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.12 (s, 1H, pyrazole H), 6.94 (d, 1H, ArH, J= 7.2 Hz), 7.28–7.36 (m, 3H, ArH), 11.14 (s, 1H, NH) ; ^{13}C NMR (100MHz, DMSO, 25 °C): δ = 13.82, 14.09, 21.65, 109.05, 115.52, 118.94, 124.57, 129.78, 139.29, 139.78, 141.93, 149.89, 158.89, 179.22

5–(3–Chloroanilino)–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazole (**4c**): Yield: Method A: 63%, m.p. 275–76 °C. Method B: 65%; m. p 275°C ; IR: 3241, 3118, 3058, 1613, 1531, 1423, 1382, 1121, 976, 801 cm^{-1} ; ^1H NMR (400 MHz, DMSO, 25 °C): δ = 2.20 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 6.14 (s, 1H, pyrazole H), 7.17(s, 1H, ArH), 7.44 (s, 2H, ArH),7.87 (1H, ArH), 11.35 (s, 1H, NH) ; ^{13}C NMR (100MHz, DMSO, 25 °C): δ = 13.83, 14.09, 109.20, 116.80, 117.87, 123.27, 131.52, 134.16, 141.07, 141.97, 150.07, 178.87

5–(4–Fluoroanilino)–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazole (**4d**): yield: Method A: 68%, m.p. 253–254 °C. Method B: 72%; m. p. 253 °C ; IR: 3271, 3218, 3036, 1628, 1589, 1501, 1441, 1393, 1218, 1106, 827 cm^{-1}; ^1H NMR (400 MHz, DMSO, 25 °C): δ = 2.19 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.12 (s, 1H, pyrazole H), 6.94 (d, 1H, ArH, J= 7.2 Hz), 7.28–7.36 (m, 3H, ArH), 11.14 (s, 1H, NH) ; ^{13}C NMR (100MHz, DMSO, 25 °C): δ = 13.82, 14.04, 109.04, 116.41, 116.64, 120.29, 136.30, 141.94, 149.86, 157.34, 158.90, 159.73, 179.25

5–(4–Bromoanilino)–3–(3,5–dimethylpyrazol–1–yl)–1,2,4–thiadiazole (**4e**): Yield: Method A: 90%, m.p. 222–223 °C. Method B: 96%; m. p 222 °C ; IR: 3241, 3181, 3048, 1609, 1557, 1479, 1397, 1300, 1110, 81 cm^{-1}; ^1H NMR (400 MHz, DMSO, 25 °C): δ = 2.19 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.12 (s, 1H, pyrazole H), 7.54–7.61(m, 4H, ArH), 11.26 (s, 1H, NH)
^{13}C NMR (100MHz, DMSO, 25 °C): δ = 13.83, 14.06, 109.09, 115.20, 120.28, 131.92, 132.61, 139.10, 141.99, 149.94, 158.86, 178.87

4. CONCLUSION

In conclusion, we have now shown that 3,5–dimethyl–1–[(*N*–arylthiocarbamoyl)amidino] pyrazoles are useful starting materials for accessing 5–anilino–1,2,4–thiadiazole derivatives, thus complementing our earlier report on their use to prepare 2,4–diaminothiazoles and 3,5–diamino–1,2,4–triazoles. We have also demonstrated that the above oxidative heterocyclization of 3,5–dimethyl–1–[(*N*–arylthiocarbamoyl) amidino] pyrazoles can effectively be achieved by mechanochemically in a green chemical approach.

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