

## Mechanochemical synthesis of novel 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles and their application in thiocarbamoylguanylations

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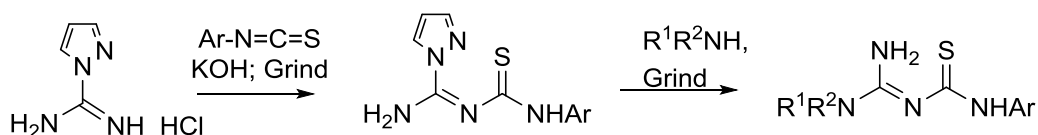
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### Abstract

Guanidines are important for a variety of reasons, including their use in medicinal and industrial applications. Mechanochemistry is being increasingly adopted as a green-chemistry technique for solvent-free organic synthesis. The synthesis of novel 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles and their use as guanylation agents for the conversion of amines to *N*-alkyl- and *N,N*-cycloalkyl-*N'*-(*N*-arylthiocarbamoyl)guanidines by solvent-based and solvent-free mechanochemical methods are described.



**Keywords:** Guanidines, mechanochemistry, thiocarbamoylamidinopyrazoles

## Introduction

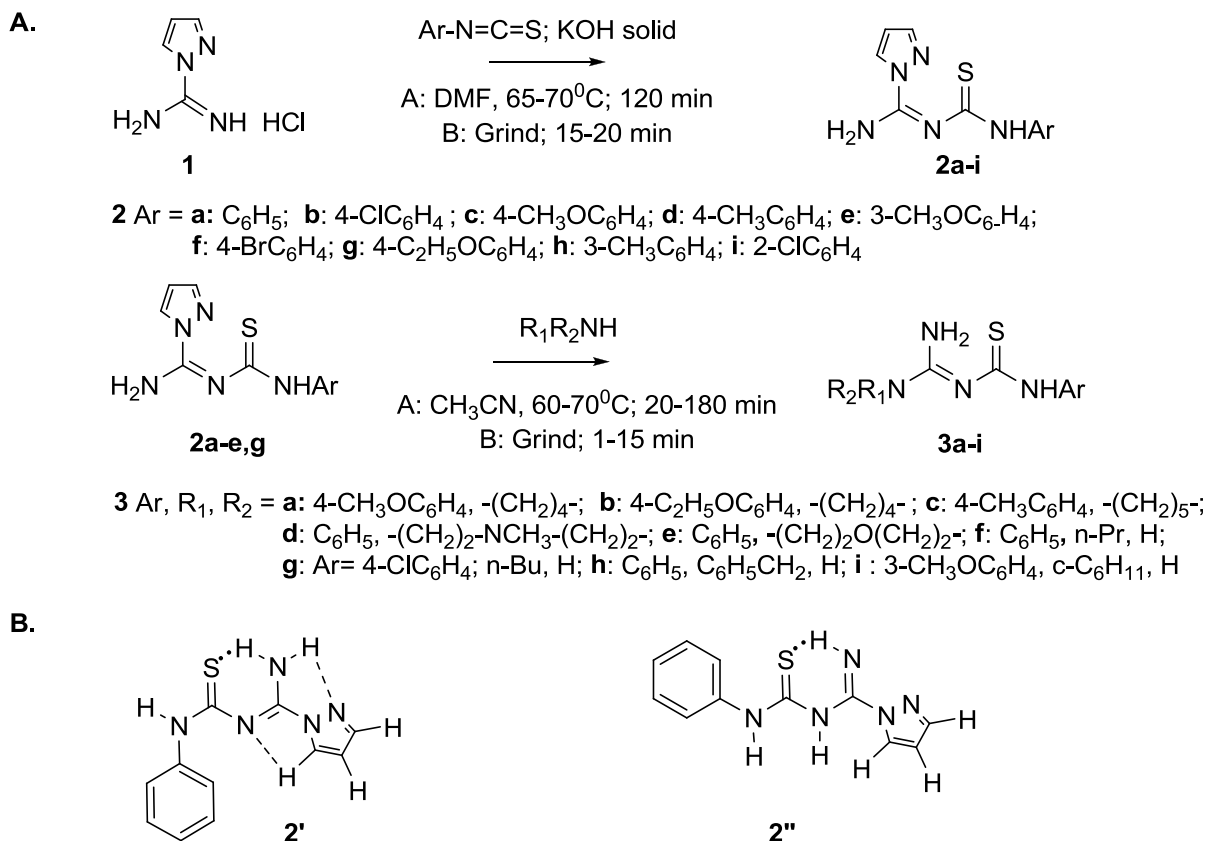
Guanidines occupy a prominent position among organic compounds, including a variety of biologically-active compounds, due to the presence of the guanidino structural motif<sup>1</sup>. Interest in guanidines also stems from their applications as super bases<sup>2</sup>, as base catalysts in organic synthesis<sup>3</sup> and as sweeteners<sup>4</sup>. Consequently, investigations on guanidine synthesis remain ever-active<sup>5</sup> and related reviews have appeared recently<sup>6</sup>. Prominent methods available for the synthesis of guanidines broadly involve the reaction of amines with thiourea derivatives such as *S*-alkylsulfanylisothiureas<sup>7</sup>, aminoiminomethane sulfonic acids<sup>8</sup>, and Boc-isothiureas<sup>9-11</sup>, the addition of amines to carbodiimides and cyanamides, and amidine group-transfer reactions. The amidine group-transfer agents used for the conversion of amines to guanidines include 1-amidinopyrazole and 1-amidino-1,2,4-benzotriazole derivatives<sup>12-16</sup>. We have earlier reported the synthesis and use of 1-[(*N*-arylthiocarbamoyl)amidino]-3,5-dimethylpyrazoles<sup>17,18</sup> and 1-*N*-arylamidino-1,2,4-benzotriazoles<sup>19</sup> for the conversion of amines to *N*-(*N*-arylthiocarbamoyl)-*N'*-substituted guanidines and *N,N'*-substituted guanidines, respectively. We now report the synthesis of hitherto undescribed 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles (**2**) and their use in the thiocarbamoylamidination of amines under mechanochemical, solid-state conditions. Mechanochemistry is now being increasingly adopted as a green-chemistry technique for solvent-free organic synthesis as attested by the appearance of recent reviews<sup>20-22</sup>. Mechanochemical methods, including grinding and ball milling, have successfully been applied to coupling, condensation, addition, substitution, oxidation, reduction and halogenation reactions, and to asymmetric synthesis<sup>23</sup>. In addition to their compatibility with green-chemistry principles, mechanochemical reactions are now known to permit synthesis of compounds and isolation of reaction intermediates arising from alternative chemical reactivity and selectivity that are inaccessible by thermal-solution chemistry methods<sup>24,25</sup>.

## Results and Discussion

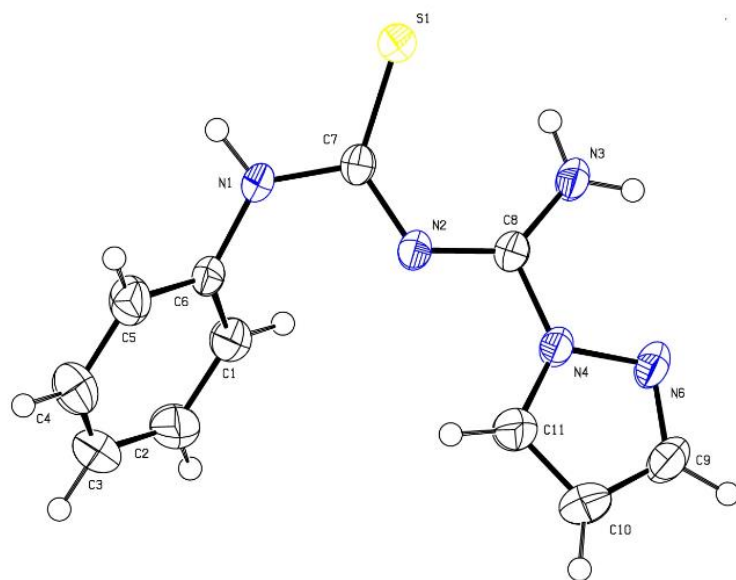
Based on the reported mechanochemical synthesis of thiourea derivatives by the reaction of amines with isothiocyanates<sup>26,27</sup>, and our recent success in the solvent-free, mechanochemical syntheses of heterocycles<sup>28</sup>, the reaction of 1-amidinopyrazole hydrochloride (**1**) with aryl isothiocyanates, in the presence of a base, was investigated using both thermal (Method A) and mechanochemical (Method B) conditions. The thermal reaction was done in *N,N*-dimethylformamide (DMF), using a modified version<sup>17</sup> of the one reported by Scott and Reilly<sup>29</sup>, by first stirring (**1**) with powdered potassium hydroxide at 0-4 °C for 20 min, and then adding aryl isothiocyanates and continuing the stirring at 65-70°C for another 2 h. The mechanochemical method required a simple grinding of (**1**) and aryl isothiocyanates for 15-20 min in the presence of solid KOH (Scheme 1). The products obtained by both methods were found to be identical by m.p., mixed m.p., TLC, and FTIR. The <sup>1</sup>H NMR spectra of the products indicated that these compounds exist in solution as more than one conformer-tautomer. Based on NMR spectral studies, the existence of such preferred conformer-tautomer systems have recently been demonstrated<sup>30</sup> for *N*-Boc-*N'*-propyl-*N''*-pyridin-2-ylguanidines and related compounds due to conformational control induced by strong intramolecular hydrogen bonding in CDCl<sub>3</sub> solution. A freezing of C=N cis ⇌ trans configurational interconversion has also been reported by NMR studies in the case of *N*-benzoyl-*N'*-pyridin-2-ylguanidines<sup>31</sup>. Thus, the product obtained from (**1**) and 4-methoxyphenyl isothiocyanate, taken as a typical example, was found to be homogeneous by TLC and HPLC analysis (data not shown), and the HRMS data were in good agreement with the proposed structure, 1-[(*N*-4-methoxyphenylthiocarbamoyl)amidino]pyrazole (**2c**). In the 400 MHz <sup>1</sup>H NMR spectrum in CDCl<sub>3</sub>, the pyrazole

ring hydrogen H-4 appeared as a pair of signals, i.e., one doublet of a doublet, and the other a broad, poorly-resolved signal, in the ratio 1.71:1 at  $\delta$  6.37 and 6.45 ppm, respectively. This assignment is based on a comparison with the  $^1\text{H}$  NMR spectral data of 1-[*N,N'*-bis-(tert-butyloxycarbonyl)amidino]pyrazole<sup>13</sup>. The other two pyrazole hydrogens, H-3 and H-5, as well as the aryl hydrogens, also exhibited multiple broadened signals. The  $^1\text{H}$  NMR spectrum of the product (**2c**) in  $\text{CD}_3\text{OD}$  was less complex, and clearly indicated the presence of at least two conformer-tautomer molecular species. Thus, in the spectrum, the three signals due to the pyrazole-ring hydrogen H-4 at  $\delta$  6.35 ppm and at  $\delta$  6.41 ppm, the two aryl hydrogens ortho to the CS-NH group at  $\delta$  7.17 ppm and  $\delta$  7.44 ppm, and the pyrazole ring hydrogen H-5 at  $\delta$  7.96 ppm and at  $\delta$  8.47 ppm appeared as pairs, and in the ratios 1.24:1, 1.28:1 and 1.33:1, respectively. These ratios seem to indicate that (**2c**) exists in  $\text{CD}_3\text{OD}$  solution as 56% of one molecular species and 44% of another. The  $^1\text{H}$  NMR spectrum of (**2g**) in  $\text{DMSO-}d_6$  also clearly showed the existence of at least two conformer-tautomer species since the  $^1\text{H}$  NMR signals of the pyrazole-ring hydrogen H-4, the two aryl hydrogens ortho to the CS-NH moiety, and the pyrazole ring hydrogen H-5 appeared as pairs in each case, and in the ratios 1.6:1, 1.48:1 and 1.43:1, respectively. A limited, variable-temperature, NMR study of (**2c**) in  $\text{CDCl}_3$  indicated a temperature-dependent broadening of signals which is suggestive of a dynamic process in solution (data not shown). The FTIR spectrum of (**2c**) recorded from the KBr-pellet method was similar to that recorded in  $\text{CHCl}_3$ , thus pointing to no significant difference in structure in solid and solution states. The HRMS spectrum of (**2c**) showed a  $[\text{M}+\text{H}]$  peak at 276.0915, which is in agreement with the calculated value of 276.0841, based on the molecular composition  $\text{C}_{12}\text{H}_{13}\text{N}_5\text{OS}$ . To obtain further insight into the structure of these products, single-crystal X-ray diffraction analysis of crystals of (**2a**), obtained from ethyl acetate/petroleum ether by slow evaporation, was done. The solid-state structure (Fig. 1) revealed the preference for the amino-thione tautomer (**2'**) with an anti-conformation along the C-N bond of the CS-NHPh moiety. An intramolecular hydrogen-bonding interaction between one hydrogen of the amino group and the thione sulfur, another weak intramolecular hydrogen-bonding interaction of the remaining hydrogen of the amino group with the  $\text{sp}^2$  nitrogen of the pyrazole ring, and yet another weak intramolecular hydrogen-bonding interaction between the C5-H hydrogen of the pyrazole ring and the  $\text{sp}^2$ -N atom of the amidine unit, lead to the conformationally-restricted conformer-tautomer (**2'**), which seems to persist in solution along with another conformer-tautomer, presumably (**2''**). The intramolecular distances, calculated based on the crystallographic data, show that the length of the  $\text{C}=\text{S}\cdots\text{H}-\text{N}$  hydrogen bond in (**2'**) to be 2.414 Å, and the  $\text{S}\cdots\text{H}-\text{N}$  bond angle to be  $132^\circ$ . The intramolecular distance between the pyrazole-ring nitrogen and the hydrogen of the amino group involved in the  $[\text{sp}^2\text{-N}\cdots\text{H}-\text{N}]$  interaction in (**2'**) is found to be 2.347 Å with a  $\text{N}\cdots\text{H}-\text{N}$  bond angle of  $105.21^\circ$ . The intramolecular distance between the C5-H hydrogen of the pyrazole ring and the  $\text{sp}^2$ -N atom of the amidine unit in (**2'**) is seen to be 2.642 Å. Interestingly, Kelly *et al.* have reported a similar intramolecular hydrogen bond between the C3-H of a pyridine ring and the  $\text{sp}^2$ -N atom of an attached guanidino group in *N,N'*-di-Boc-*N''*-pyridin-2-ylguanidine<sup>30</sup> and *N,N'*-di-Boc-*N''*-phenylguanidine.<sup>30</sup> Although details of intermolecular hydrogen bonding between N-H hydrogen and the sulfur atom of a thione group  $\text{C}=\text{S}$  flanked by two nitrogen atoms, as in thioureas, are known<sup>32,33</sup>, the corresponding information regarding intramolecular hydrogen bonding seems sparse. The length of the thioureido  $\text{C}=\text{S}\cdots\text{H}-\text{N}$  intermolecular hydrogen bond has been reported to be 2.51 Å<sup>32</sup>. It is now suggested that the presence of the conformer-tautomers (**2'**) and (**2''**) in solution, with the latter predominating, could account for the appearance of more than one signal of the hydrogens of the pyrazole and aryl rings, and their broadening in the  $^1\text{H}$  NMR spectra. Furthermore, the presence of the conformer (**2'**) seems to account for the prominent deshielding of the pyrazole ring C5-H hydrogen, due to the influence of the juxtaposed phenyl ring, and the intramolecular hydrogen-bonding interaction between the C5-H hydrogen of the pyrazole ring and the  $\text{sp}^2$ -N atom of the amidine unit. Such a remarkable deshielding effect, along with peak broadening, has been

reported by Kelly *et al.* for the C3-H hydrogen of the pyridine ring in *N,N'*-di-Boc-*N''*-pyridin-2-ylguanidine due to intramolecular hydrogen bonding between the C3-H hydrogen of the pyridine ring and the  $sp^2$ -N atom of the *N,N'*-di-Boc-guanidino group.<sup>30</sup> Similar deshielding and peak broadening due to a possible interaction between the C5-H hydrogen of the pyrazole ring and the  $sp^2$ -N atom of the amidine unit, however, has not been reported in the  $^1\text{H}$  NMR spectrum of 1-(*N,N'*-di-Boc-amidino)pyrazole<sup>13</sup>.



**Scheme 1. A.** Synthesis of 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles (**2a-i**) and *N*-alkyl- and *N,N*-cycloalkyl-*N'*-(*N*-arylthiocarbamoyl)guanidines (**3a-i**). **B.** Proposed conformer-tautomer pair of 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles (**2'**) and (**2''**) in solution.



**Figure 1.** Molecular structure **2'** of 1-[(*N*-phenylthiocarbamoyl)amidino]pyrazole (**2a**) based on single-crystal XRD analysis.

We next explored the reaction of 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles (**2**) with primary and cyclic secondary alkylamines under thermal (Method A) and mechanochemical (Method B) conditions which afforded *N*-alkyl-*N'*-(*N*-arylthiocarbamoyl)guanidines (**3a-d**) and *N*-(*N*-arylthiocarbamoyl)-*N'*,*N'*-di-substituted guanidines (**3e-i**) (Scheme 1). The compounds **3a-i** were characterized by IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS spectral studies. The results indicate that the reaction occurs chemoselectively by the scission of the bond between the pyrazole ring and the amidino moiety. These results attest to the use of 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles (**2**) in the preparation of functionalized guanidines. Their use in heterocycle synthesis is currently under investigation.

## Conclusions

In conclusion, we now report the novel 1-amidinopyrazole-based guanylation reagents 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles (**2**), prepared from 1-amidinopyrazole hydrochloride (**1**) and aryl isothiocyanates by a green-chemistry mechanochemical approach in fairly good yield. We have also investigated the guanylation reaction of primary and cyclic secondary alkylamines with 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles (**2**) using mechanochemical conditions, leading to the formation of *N*-alkyl-*N'*-(*N*-arylthiocarbamoyl)guanidines (**3a-d**) and *N,N*-disubstituted-*N'*-(*N*-arylthiocarbamoyl)guanidines (**3e-i**) in good yields.

## Experimental Section

**General.** Melting points were uncorrected and determined by open capillary method. The thin-layer chromatographic (TLC) analyses were performed using silica gel 60 F<sub>254</sub> TLC aluminium sheets purchased from E. Merck, Mumbai, India. The FTIR spectra were recorded on Thermo Nicolet Avatar 370 and Agilent

Technologies spectrophotometers. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$ ,  $\text{DMSO-}d_6$  and  $\text{CD}_3\text{OD}$  on a Bruker DPX 400 MHz NMR spectrometer at room temperature using TMS as the internal-reference standard. Chemical shifts are given in ppm and the coupling constants in Hz. The HRMS-ESI analyses were performed on an Agilent 6520 QTOF-MS/MS system. The crystal structure of (**2a**) was determined using a Bruker Kappa Apex II Single-Crystal X-ray Diffractometer and the supplementary crystallographic data can be obtained free of charge from Cambridge Crystallographic Data Centre under the deposition number CCDC 1573139. All chemicals used were from Sigma Aldrich and E. Merck, India.

**General experimental procedure for the preparation of 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles (2a-i) by method A (thermal method).** Powdered potassium hydroxide (112 mg, 2 mmol) was added to DMF (5 mL) at 0 °C, followed by 1-amidinopyrazole hydrochloride (**1**) (292 mg, 2 mmol). The mixture was stirred in ice for 20 min to obtain a clear solution. To this solution, aryl isothiocyanate (2 mmol) was added with stirring. The ice bath was replaced by a hot-water bath at 65-70 °C and the stirring was continued for another 2 h. The mixture was poured into ice-water (50 mL), kept for coagulation of the precipitate which was then collected, washed with petroleum ether, and crystallized from an ethanol-water (1: 1) mixture.

**General experimental procedure for the preparation of 1-[(*N*-arylthiocarbamoyl)amidino]pyrazoles (2a-g) by method B (mechanochemical method).** Powdered potassium hydroxide (112 mg, 2 mmol) was added to 1-amidinopyrazole hydrochloride (**1**) (292 mg, 2 mmol) in an agate mortar and the mixture was ground with an agate pestle for 1-3 min. To this mixture, aryl isothiocyanate (2 mmol) was added and the grinding continued at room temperature for 15-20 min. The oily emulsion first formed subsequently solidified and the solid was worked up by triturating with petroleum ether, followed by water. The product was collected by filtration and purified by crystallization from an ethanol-water mixture (1:1).

**1-[(*N*-Phenylthiocarbamoyl)amidino]pyrazole (2a).** Light yellow crystals. yield: 343 mg, 70% (Method A); 343 mg, 70% (Method B). mp 120-122 °C. IR (solid, KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3292, 3253, 3018, 1637, 1510, 696. *It may be noted that as the  $^1\text{H}$  NMR spectra of 2a-i are composite spectra of more than one conformer-tautomer, the hydrogen count has been normalized based on the composite signals of pyrazole ring H-4 hydrogen in the range  $\delta_{\text{H}}$  6.3-6.7 ppm and attributed to one hydrogen. Consequently, the hydrogen count associated with the  $^1\text{H}$  NMR signals reported below are fractional<sup>30</sup>.*  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  6.40 [broad singlet (bs), 0.68H], 6.46 (bs, 0.32H), 7.15-7.30 (m, 0.94H), 7.30-7.50 (m, 2.38H), 7.60-7.95 (m, 2.57H), 8.10 (s, 0.71H), 8.34 (bs, 0.68H), 8.48 (bs, 0.34H), 8.61 (bs, 0.30H), 11.09 (bs, 1.0H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  109.5, 123.5, 124.3, 125.4, 128.7, 143.7, 154.1, 188. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{11}\text{N}_5\text{S}$  246.0735  $[\text{M}+\text{H}]^+$ ; found 246.0804.

**1-[(*N*-4-Chlorophenylthiocarbamoyl)amidino]pyrazole (2b).** Light yellow crystals. yield: 463 mg, 83% (Method A); 419 mg, 75% (Method B). mp 165-167 °C. IR (solid, KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3307, 3238, 3095, 1639, 1521, 765.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  6.40-6.55 (m, 1.0H), 7.25-7.45 (m, 4.08H), 7.55-7.70 (bs, 0.80H), 7.73 (s, 1.25H), 7.83 (bs, 0.71H), 8.08 (bs, 0.67H), 8.29 (bs, 0.62H), 8.46 (bs, 0.32H), 8.56 (bs, 0.18H), 11.13 (bs, 1.03H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  109.7, 124.7, 125.4, 126.6, 128.5, 128.8, 129.8, 143.9. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{10}\text{ClN}_5\text{S}$  280.0345  $[\text{M}+\text{H}]^+$ ; found 280.0419.

**1-[(*N*-4-Methoxyphenylthiocarbamoyl)amidino]pyrazole (2c).** Light yellow crystals. yield: 413 mg, 75% (Method A); 402 mg, 73% (Method B). mp 154-156 °C. IR (solid, KBr,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3400, 3309, 3076, 2962, 1662, 1620, 1500, 1332, 1253, 1058, 1031, 948, 827, 769, 725. IR ( $\text{CHCl}_3$ ,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3400, 3310, 3059, 2964, 1659, 1623, 1519, 1486, 1331, 1060, 1027, 948, 826, 768, 722.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.83 (bs, 3.12H), 6.35-6.40 (m, 0.63H), 6.42-6.50 (b, 0.37H), 6.85-7.00 (m, 2.15H), 7.25-7.35 (m, 1.70H), 7.48 (d, 0.68H,  $J$  8.8 Hz), 7.65-7.85 (bm, 1.82H), 8.04 (d, 0.63H,  $J$  2.4 Hz), 8.28 (b, 0.64H), 8.44 (d, 0.63H,  $J$  2.4 Hz), 10.95-11.25 [broad multiplet (bm), 0.97H].  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta_{\text{H}}$  3.70 (m, 3.25H), 6.35 (dd, 0.55H,  $J$  2.8 Hz,  $J$  1.6 Hz), 6.41

(dd, 0.45H, *J* 2.8 Hz, *J* 1.6 Hz), 6.78-6.85 (m, 2.15H), 7.17 (dd, 1.10H, *J* 7.2 Hz, *J* 2.0 Hz), 7.44 (dd, 0.86H, *J* 7.2 Hz, *J* 2.0 Hz), 7.62-7.68 (m, 1.0H), 7.96 (d, 0.56H, *J* 2.4 Hz), 8.47 (d, 0.42H, *J* 2.4 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ<sub>c</sub>: 55.4, 55.5, 109.0, 109.3, 113.8, 114.1, 125.3, 126.5, 128.0, 128.1, 131.7, 143.3, 150.9, 157.4, 187.7. HRMS (ESI): *m/z* calcd. for C<sub>12</sub>H<sub>13</sub>N<sub>5</sub>OS 276.0841 [M+H]<sup>+</sup>; found 276.0915.

**1-[(*N*-4-Methylphenylthiocarbamoyl)amidino]pyrazole (2d).** Light yellow crystals. yield: 337 mg, 65% (Method A); 332 mg, 64% (Method B). mp 130-132 °C. IR (solid, KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3223, 3064, 1641, 1523, 812. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) : δ<sub>H</sub> 2.25-2.35 (m, 2.93H), 6.59 (s, 0.62H), 6.63 (bs, 0.38H), 7.10-7.20 (m, 2.01H), 7.31 (d, 1.23H, *J* 8.4 Hz), 7.50-7.60 (m, 0.73H), 7.92 (s, 0.97H), 8.09 (d, 0.59H, *J* 2.4 Hz), 8.57 (b, 0.36H), 9.20-9.35 (bs, 0.19H), 10.7-10.9 (b, 0.53H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ<sub>c</sub>: 20.5, 108.9, 109.5, 123.2, 123.2, 123.6, 128.5, 128.8, 133.6, 136.6, 136.3, 136.7, 143.6, 143.8, 151.4, 152.7, 185.9, 187.3. HRMS (ESI): *m/z* calcd. for C<sub>12</sub>H<sub>13</sub>N<sub>5</sub>S 260.0892 [M+H]<sup>+</sup>; found 260.0969.

**1-[(*N*-3-Methoxyphenylthiocarbamoyl)amidino]pyrazole (2e).** Light yellow crystals. yield: 347 mg, 63% (Method A); 374 mg, 68% (Method B). mp 125-127 °C. IR (solid, KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3344, 3072, 1662, 1575, 1325, 825. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 3.70-3.95 (bm, 3.10H), 6.35-6.55 (m, 1.00H), 6.70-6.85 (bm, 1.00H), 6.90-7.05 (bm, 1.43H), 7.08-7.20 (bs, 0.32H), 7.20-7.35 (m, 0.81H), 7.48 (bs, 0.32H), 7.72 (bs, 1.27H), 7.81 (bs, 0.72H), 8.18 (bs, 0.71H), 8.40-8.60 (bm, 0.64H), 11.10 (bm, 1.00H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>c</sub> 55.4, 109.3, 109.5, 110.8, 115.6, 128.8, 129.4, 143.8, 159.9, 188.1. HRMS (ESI): *m/z* calcd. for C<sub>12</sub>H<sub>13</sub>N<sub>5</sub>OS 276.0841 [M+H]<sup>+</sup>; found 276.0907.

**1-[(*N*-4-Bromophenylthiocarbamoyl)amidino]pyrazole (2f).** Light yellow crystals. yield: 446 mg, 69% (Method A); 420 mg, 65% (Method B). mp 155-156 °C. IR (neat, ν<sub>max</sub>, cm<sup>-1</sup>): 3313, 3250, 3019, 1632, 1587. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) : δ<sub>H</sub> 6.46 (bs, 1.00H), 7.20-7.35 (m, 1.61H), 7.45-7.65 (m, 3.01H), 7.75 (s, 1.28H), 7.80-8.00 (bs, 0.95H), 8.11 (bs, 0.77H), 8.30-8.60 (bm, 1.40H), 10.90-11.30 (b, 0.97H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>c</sub> 109.7, 120.7, 121.8, 124.9, 126.8, 128.7, 131.8, 133.3, 137.5, 143.9, 154.4, 187.7. HRMS (ESI): *m/z* calcd. for C<sub>11</sub>H<sub>10</sub>BrN<sub>5</sub>S 323.9840 [M+H]<sup>+</sup>; found 323.9890.

**1-[(*N*-4-Ethoxyphenylthiocarbamoyl)amidino]pyrazole (2g).** Light yellow crystals. yield: 410 mg, 71% (Method A); 434 mg, 75% (Method B). mp 110-112 °C. IR (solid, KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3223, 3064, 1641, 1523, 1367, 812. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) : δ<sub>H</sub> 1.20-1.35 (m, 3.01H), 3.85-4.15 (m, 2.04H), 6.58 (bs, 0.58H), 6.70 (m, 0.42H), 6.85-6.95 (m, 2.02H), 7.25-7.35 (m, 1.19H), 7.50-7.60 (m, 0.81H), 7.91 (d, 0.97H, *J* 0.4 Hz), 8.06 (t, 0.57H, *J* 2.8 Hz), 8.57 (d, 0.40H, *J* 2.4 Hz), 9.21 (bs, 0.21H), 10.58 (bs, 0.40H), 10.70 (bs, 0.19H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) : δ<sub>c</sub> 14.6, 63.1, 108.9, 109.5, 113.9, 124.7, 124.8, 125.4, 125.5, 128.5, 131.7, 132.2, 132.3, 143.4, 143.7, 151.4, 152.6, 155.4, 155.9, 185.5, 187.2. HRMS (ESI): *m/z* calcd. for C<sub>13</sub>H<sub>15</sub>N<sub>5</sub>OS 290.0997 [M+H]<sup>+</sup>; found 290.1081.

**1-[(*N*-3-Methylphenylthiocarbamoyl)amidino]pyrazole (2h).** Light yellow crystals. yield: 368 mg, 71% (Method A); mp 112-114 °C. IR (solid, KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3209, 3015, 1632, 1543, 782. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) : δ<sub>H</sub> 2.63 (s, 2.86H), 6.35-6.50 (bm, 1.00H), 6.95-7.10 (bm, 1.00H), 7.15-7.35 (m, 2.69H), 7.40-7.50 (m, 0.59H), 7.71 (s, 1.12H), 7.79 (bs, 1.12H), 8.12 (bs, 0.70H), 8.35-8.45 (bm, 1.00H), 8.52 (bs, 0.28H), 10.85-11.30 (b, 1.00H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>c</sub> 21.4, 109.4, 120.6, 123.9, 126.1, 128.5, 128.7, 138.4, 143.7, 154.0, 187.7. HRMS (ESI): *m/z* calcd. for C<sub>12</sub>H<sub>13</sub>N<sub>5</sub>S 260.0892 [M+H]<sup>+</sup>; found 260.0960.

**1-[(*N*-2-Chlorophenylthiocarbamoyl)amidino]pyrazole (2i).** Light yellow crystals. yield: 456 mg, 82% (Method A); mp 147-150 °C. IR (solid, KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3220, 3022, 1640, 1587, 749. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) : δ<sub>H</sub> 6.50-6.60 (bs, 1.00H), 7.10-7.20 (bm, 1.68H), 7.22-7.35 (m, 1.03H), 7.50-7.65 (bs, 0.74H), 7.65-8.00 (bm, 1.84H), 8.16 (bs, 0.75H), 8.20-8.60 (bm, 1.23H), 10.95-11.20 (bs, 1.03H). <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>): δ<sub>c</sub> 109.7, 123.7, 125.1, 128.7, 129.7, 134.3, 139.4, 143.9, 186.2. HRMS (ESI): *m/z* calcd. for C<sub>11</sub>H<sub>10</sub>ClN<sub>5</sub>S 280.0345 [M+H]<sup>+</sup>; found 280.0411.

**General experimental procedure for the preparation of *N*-alkyl and *N,N*-cycloalkyl-*N'*-(*N*-arylthiocarbamoyl)guanidines (3a-i) by method A (thermal method).** To a solution of 1-[(*N*-arylthiocarbamoyl)amidino]pyrazole (**2**) (1 mmol) in acetonitrile (3 mL), the respective amine (10 mmol) was added. The mixture was kept at 60-70 °C for 20 min to 3 h. The solvent was removed under reduced pressure and the syrupy residue obtained was extracted with petroleum ether. The crude solid obtained was then crystallized from ethanol-water (1:1).

**General experimental procedure for the preparation of *N*-alkyl- and *N,N*-cycloalkyl-*N'*-(*N*-arylthiocarbamoyl)guanidines (3a-i) by method B (mechanochemical method):** 1-[(*N*-arylthiocarbamoyl)amidino]pyrazole (**2**) (1 mmol) was ground with the respective amine (10 mmol) in an agate mortar for 1-15 min. The whole pasty mass soon turned into a solid mass and was triturated with petroleum ether. The crude solid obtained was crystallized from ethanol-water (1:1).

**1-[(*N*-4-Methoxyphenylthiocarbamoyl)amidino]pyrrolidine (3a).** Colourless crystals. yield: 253 mg, 91% (Method A); 256 mg, 92% (Method B). mp 181-183 °C. IR (neat,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3371, 3122, 2961, 1598, 1538, 1348, 733.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  1.80-2.20 (m, 4H, pyrrolidine  $\text{CH}_2$ ), 3.20-3.60 (m, 4H, pyrrolidine  $\text{N-CH}_2$ ), 3.78 (s, 3H,  $\text{OCH}_3$ ), 6.81 (d, 2H,  $J$  8.6 Hz, ArH), 7.36 (d, 2H,  $J$  8.6 Hz, ArH), 7.71 (s, 2H, NH).  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  25.2, 45.8, 55.4, 113.5, 114.9, 121.5, 123.8, 132.9, 158.2, 182.5. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{18}\text{N}_4\text{OS}$  279.1201  $[\text{M}+\text{H}]^+$ ; found 279.1332.

**1-[(*N*-4-Ethoxyphenylthiocarbamoyl)amidino]pyrrolidine (3b).** Colourless crystals. yield: 254 mg, 87% (Method A); 263 mg, 90% (Method B). mp 170-174 °C. IR (neat,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3423, 3222, 2969, 1590, 1553, 1348, 815.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  1.40 (t, 3H,  $J$  6.9 Hz,  $\text{CH}_3$ ), 1.98-2.10 (m, 4H, pyrrolidine  $\text{CH}_2$ ), 3.20-3.60 (m, 4H, pyrrolidine  $\text{N-CH}_2$ ), 4.00 (q, 2H,  $J$  6.9 Hz,  $\text{OCH}_2$ ), 6.80 (d, 2H,  $J$  8.2 Hz, ArH), 7.35 (d, 2H,  $J$  8.2 Hz, ArH), 7.68 (s, 2H, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  14.9, 25.2, 45.8, 63.6, 114.1, 123.8, 132.8, 155.4, 158.2, 182.2. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{20}\text{N}_4\text{OS}$  293.1358  $[\text{M}+\text{H}]^+$ ; found 293.1427.

**1-[(*N*-4-Methylphenylthiocarbamoyl)amidino]piperidine (3c).** Colourless crystals. yield: 177 mg, 64% (Method A); 193 mg, 70% (Method B). mp 132-133 °C. IR (neat,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3222, 2917, 1590, 1542, 979, 733.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  1.62-1.69 (m, 6H, piperidine  $\text{CH}_2$ ), 2.32 (s, 3H,  $\text{CH}_3$ ), 3.40-3.60 (m, 4H, piperidine  $\text{N-CH}_2$ ), 7.08-7.10 (m, 2H, ArH), 7.30-7.33 (m, 2H, ArH), 7.79 (s, 2H, NH) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  20.9, 24.2, 25.5, 45.4, 122.2, 128.9, 133.5, 136.9, 159.0, 182.4. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{20}\text{N}_4\text{S}$  277.1409  $[\text{M}+\text{H}]^+$ ; found 277.1487.

**1-[(*N*-Phenylthiocarbamoyl)amidino]-4-methylpiperazine (3d).** Colourless crystals. yield: 216 mg, 78% (Method A); 205 mg, 74% (Method B). mp 138-140 °C. IR (neat,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3202, 2928, 1598, 1553, 748.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.33 (s, 3H,  $\text{N-CH}_3$ ), 2.43 (t, 4H,  $J$  5 Hz, piperazine  $\text{CH}_2-\text{NCH}_3$ ), 3.56 (t, 2H,  $J$  5 Hz, piperazine  $\text{CH}_2-\text{N}$ ), 7.10 (t, 1H,  $J$  7.2 Hz, ArH), 7.29-7.32 (m, 2H, ArH), 7.36-7.45 (m, 2H, ArH), 7.90 (s, 3H, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  43.9, 45.9, 54.3, 122.7, 124.2, 128.4, 139.2, 159.4, 182.2. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{19}\text{N}_5\text{S}$  278.1361  $[\text{M}+\text{H}]^+$ ; found 278.1429.

**1-[(*N*-Phenylthiocarbamoyl)amidino]morpholine (3e).** Colourless crystals. yield: 180 mg, 68% (Method A); 172 mg, 65% (Method B). mp 152-155 °C. IR (neat,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3215, 2965, 1602, 1549, 741.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.40-3.60 (m, 4H, morpholine  $\text{N-CH}_2$ ), 3.71-3.73 (m, 4H, morpholine  $\text{O-CH}_2$ ), 7.11-7.37 (m, 5H, ArH), 7.92 (s, 3H, NH) ppm.  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  44.1, 66.2, 118.2, 122.8, 124.4, 128.5, 139.0, 159.6, 183.7. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{12}\text{H}_{16}\text{N}_4\text{OS}$  265.1045  $[\text{M}+\text{H}]^+$ ; found 265.1121.

***N*-(Phenylthiocarbamoyl)-*N'*-*n*-propylguanidine (3f).** Colourless crystals. yield: 168 mg, 71% (Method A); 172 mg, 73% (Method B). mp 112-115 °C. IR (neat,  $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3241, 2958, 2924, 1602, 1538, 726.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  1.03 (t, 3H,  $J$  7.3 Hz,  $\text{CH}_3$ ), 1.68 (m, 2H,  $\text{CH}_2$ ), 3.17 (q, 2H,  $J$  6.8 Hz,  $\text{CH}_2-\text{N}$ ), 6.45 (s, 1H, NH), 7.09 (t, 1H,  $J$  7.7 Hz, ArH), 7.31 (t, 2H,  $J$  7.7 Hz, ArH), 7.46 (d, 2H,  $J$  7.7 Hz, ArH), 7.84 (s, 1H, NH), 8.42 (s, 1H,



NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  11.5, 22.2, 43.4, 122.4, 124.1, 128.5, 139.2, 160.5, 183.7. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{16}\text{N}_4\text{S}$  237.1096  $[\text{M}+\text{H}]^+$ ; found 237.1173.

**N-n-Butyl-N'-(4-chlorophenylthiocarbamoyl)guanidine (3g)**. Colourless crystals. yield: 185 mg, 65% (Method A); 182 mg, 64% (Method B). mp 114-115 °C. IR (neat,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3382, 2954, 2924, 1605, 1516, 725.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  0.98 (t, 3H,  $J$  7.4 Hz,  $\text{CH}_3$ ), 1.45-1.48 (m, 2H,  $\text{CH}_2$ ), 1.64-1.67 (m, 2H,  $\text{CH}_2$ ), 3.21 (q, 2H,  $J$  5.2 Hz,  $\text{CH}_2\text{-N}$ ), 6.40 (s, 1H, NH), 7.24-7.29 (m, 2H, ArH), 7.41 (d, 2H,  $J$  8.8 Hz, ArH), 7.82 (s, 1H, NH), 8.467-8.51 (m, 1H, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  13.6, 20.1, 30.8, 41.4, 123.5, 128.5, 137.7, 160.5, 184.0. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{12}\text{H}_{17}\text{ClN}_4\text{S}$  285.0862  $[\text{M}+\text{H}]^+$ ; found 285.0924.

**N-Benzyl-N'-(phenylthiocarbamoyl)guanidine (3h)**. Colourless crystals. yield: 213 mg, 75% (Method A); 219 mg, 77% (Method B). mp 112-115 °C. IR (neat,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3364, 3245, 3133, 1587, 1538, 733.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  4.46 (s, 2H,  $\text{CH}_2$ ), 6.90-7.10 (bm, 1H, NH), 7.24-7.44 (m, 10H, ArH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  45.4, 118.3, 122.5, 127.1, 128.2, 128.6, 129.1, 129.7, 138.9, 160.6, 183.85. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{16}\text{N}_4\text{S}$  285.1096  $[\text{M}+\text{H}]^+$ ; found 285.1167.

**N-Cyclohexyl-N'-(3-methoxyphenylthiocarbamoyl)guanidine (3i)**. Colourless crystals. yield: 205 mg, 67% (Method A); 199 mg, 65% (Method B). mp 147-148 °C. IR (neat,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3341, 2932, 2846, 1587, 1553, 733.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  0.80-2.1 (m, 10H, cyclohexyl  $\text{CH}_2$ ), 3.20-3.60 (m, 1H, cyclohexyl  $\text{CH-N}$ ), 3.70-3.82 (m, 3H,  $\text{OCH}_3$ ), 6.64-6.67 (m, 1H, ArH), 7.00 (d, 1H,  $J$  8 Hz, ArH), 7.14 (s, 1H, ArH), 7.20 (t, 1H,  $J$  8 Hz, ArH), 7.50-8.85 (bs, 1H, NH).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  24.3, 25.3, 32.7, 33.5, 50.6, 55.3, 104.2, 109.3, 110.5, 114.9, 129.2, 140.0, 159.8, 182.8. HRMS (ESI):  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{22}\text{N}_4\text{OS}$  307.1514  $[\text{M}+\text{H}]^+$ ; found 307.1595.

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## Supplementary Material

The  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and mass spectra of **2a-i** and **3a-i** are presented in the supplementary material.

## References

- Berlinck, R. G. S.; Bertonha, A. F.; Takaki, M.; Rodriguez, J. P. G. *Nat. Prod. Rep.* **2017**, *34*, 1264-1301. <https://doi.org/10.1039/C7NP00037E>
- Vazdar, K.; Kunetskiy, R.; Saame, J.; Kaupmees, K.; Leito, I.; Jahn, U. *Angew. Chem. Int. Ed.* **2013**, *52*, 1-5. <https://doi.org/10.1002/anie.201209858>
- Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737-752. <https://doi.org/10.1055/s-2006-926325>
- Ritter, S. K. *Chem. Eng. News* **2014**, *92*, 11-17.
- Zhang, W.X.; Xu, L.; Xi, Z. *Chem. Commun.* **2015**, *51(2)*, 254-265. <https://doi.org/10.1039/C4CC05291A>

6. Moreno, C. A.; Antinolo, A.; Hermosilla, F. C.; Otero, A. *Chem. Soc. Rev.* **2014**, *43*, 3406-3425.  
<https://doi.org/10.1039/C4CS00013G>
7. Kent, D. R.; Cody, W. L.; Doherty, A. M. *Tetrahedron Lett.* **1996**, *37*, 8711-8714.  
[https://doi.org/10.1016/S0040-4039\(96\)02022-9](https://doi.org/10.1016/S0040-4039(96)02022-9)
8. Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. N.; Mills, J. E. *J. Org. Chem.* **1986**, *51*, 1882-1884.  
<https://doi.org/10.1021/jo00360a040>
9. Guo, Z-X.; Cammidge, A. N.; Horwell, D. C. *Synth. Commun.*, **2000**, *30*, 2933-2943.  
<https://doi.org/10.1080/00397910008087443>
10. Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677-7680.  
[https://doi.org/10.1016/S0040-4039\(00\)61537-X](https://doi.org/10.1016/S0040-4039(00)61537-X)
11. Iwanowicz, E. J.; Poss, M. A.; Lin, J. *Synth. Commun.* **1993**, *23*, 1443-1445.  
<https://doi.org/10.1080/00397919308011234>
12. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497-2502.  
<https://doi.org/10.1021/jo00034a059>
13. Drake, B.; Patek, M.; Lebl, M. *Synthesis* **1994**, *6*, 579-582.  
<https://doi.org/10.1055/s-1994-25527>
14. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389-3392.  
[https://doi.org/10.1016/S0040-4039\(00\)79163-5](https://doi.org/10.1016/S0040-4039(00)79163-5)
15. Mitchinson, A.; Golding, B. T.; Griffin, R. J.; O'Sullivan, M. C. *J. Chem. Soc., Chem. Commun.* **1994**, *0*, 2613-2614.  
<https://doi.org/10.1039/c39940002613>
16. Katritzky, A. R.; Parris, R. L.; Allin, S. M.; Steel, P. J. *Synth. Commun.* **1995**, *25*, 1173-1186.  
<https://doi.org/10.1080/00397919508012681>
17. Jenardanan, G. C.; Francis, M.; Deepa, S.; Rajasekharan, K. N. *Synth. Commun.* **1997**, *27*, 3457-3462.  
<https://doi.org/10.1080/00397919708005647>
18. Francis, M.; Deepa, S.; Sreekala, S.; Rajasekharan, K. N. *Synth. Commun.* **1997**, *27*, 3463-3470.  
<https://doi.org/10.1080/00397919708005648>
19. Philip, S. K.; Rajasekharan, K. N. *Synth. Commun.* **2011**, *41*, 1593-1602.  
<https://doi.org/10.1080/00397911.2010.488312>
20. Tan, D.; Friščić, F. *Eur. J. Org. Chem.* **2018**, 18-33.  
<https://doi.org/10.1002/ejoc.201700961>
21. Achar, T. K.; Bose, A.; Mal, P.; Beilstein. *J. Org. Chem.* **2017**, *13*, 1907-1931.  
<https://doi.org/10.3762/bjoc.13.186>
22. Baig, R. B. N.; Varma, R. S. *Chem. Soc. Rev.* **2012**, *41*, 1559-1584.  
<https://doi.org/10.1039/C1CS15204A>
23. Wang, G. W. *Chem. Soc. Rev.* **2013**, *42*, 7668-7700.  
<https://doi.org/10.1039/c3cs35526h>
24. Hernández, J. G.; Bolm, C. *J. Org. Chem.* **2017**, *82*, 4007-4019.
25. Jean-Louis, D.; Tomislav, F. *ACS Cent. Sci.* **2017**, *3*, 13-19.  
<https://doi.org/10.1021/acscentsci.6b00277>
26. Štrukil, V.; Beilstein. *J. Org. Chem.* **2017**, *13*, 1828-1849.  
<https://doi.org/10.3762/bjoc.13.178>
27. Tan, D.; Štrukil, V.; Mottillo, C.; Tomislav, F. *Chem. Commun.* **2014**, *50*, 5248-5250.  
<https://doi.org/10.1039/C3CC47905F>

28. Sherin, D. R.; Thomas, S. G.; Rajasekharan, K. N. *Het. Commun.* **2015**, *21*, 381-385.
29. Scott, F. L.; Reilly, J. *J. Am. Chem. Soc.* **1952**, *74*, 4562-4566.  
<https://doi.org/10.1021/ja01138a032>
30. Kelly, B.; O'Donovan, D. H.; O'Brien, J.; McCabe, T.; Blanco, F.; Rozas, I. *J. Org. Chem.* **2011**, *76*, 9216–9227.  
<https://doi.org/10.1021/jo200954c>
31. Cunha, S.; Costa, M. B.; Napolitano, H. B.; Lariucci, C.; Vencato, I. *Tetrahedron* **2001**, *57*, 1671-1675.  
[https://doi.org/10.1016/S0040-4020\(00\)01168-6](https://doi.org/10.1016/S0040-4020(00)01168-6)
32. Allen, F. H.; Bird, C. M.; Rowland, R. S.; Raithby, P. R. *Acta Cryst.* **1997**, *B53*, 680-695.  
<https://doi.org/10.1107/S0108768197002656>
33. Wood, P. A.; Pidcock, E.; Allen, F. H. *Acta Cryst.* **2008**, *B64*, 491-496.  
<https://doi.org/10.1107/S0108768108015437>