A new practical synthesis of 3-amino-substituted 5-aminopyrazoles and their tautomerism

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Abstract

It was found that 3-amino-substituted 5-aminopyrazoles could be effectively prepared via hydrolytic decarboxylation of the corresponding 3,5-diaminopyrazole-4-carboxylates **5** under microwave irradiation. The reactions required short time (4 min) and were successfully reproduced in a larger scale and under conventional heating mimicking the microwave heating pattern. X-ray crystallography identified two different types of tautomers in crystals of related 5-aminopyrazoles with *p*-toluidyl and *p*-anisidyl moieties at the position 3, respectively.

1. Introduction

5-Aminopyrazoles have been well recognised as biologically active compounds and efficient building blocks for the construction of fused heterocyclic molecules of high medicinal value.[1] Recent studies demonstrated an interesting biological profile for 3,5-diaminopyrazole (**1**) (Fig. 1).[2] Hoffmann-La Roche patented 5-amino-3-arylaminopyrazoles (e.g. **2**) as antiviral agents, particularly useful for the treatment of hepatitis C virus infection.[3] Some 3-amino-substituted 5-aminopyrazoles of general structure **3** were also mentioned in patents as building blocks for the construction of bioactive compounds.[4] Surprisingly, information on the synthesis of such non-symmetrically substituted 3,5-diaminopyrazoles is rather scarce. The methods earlier developed for the preparation of 3-amino-substituted 5-aminopyrazoles **3** are limited to heterocyclizations of *N*-substituted cyanoacetimidate esters or amides of cyanothioacetic acid in their reactions with hydrazine.[5,6] The main drawbacks of these synthetic approaches included relatively difficult accessibility of starting materials and low yields.[3,5,6]

In our program on the synthesis of new purine-like heterocycles[7] we required 3-amino-substituted 5-aminopyrazoles **3** as synthons for further reactions.[8] That led us to the development of the described here practical method for the synthesis of compounds **3**. Our interest towards prototropic tautomerism in azoles[9] prompted us to investigate this phenomenon *viz*. tautomeric preferences in the representative compounds **3** using X-ray crystallography.

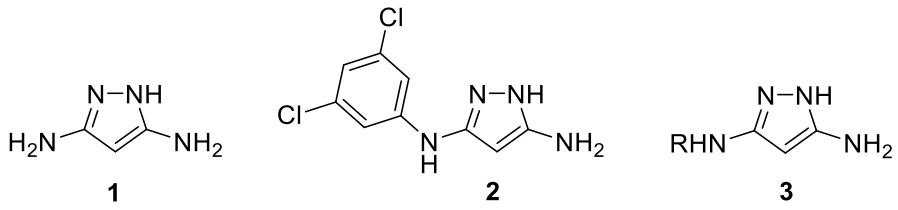
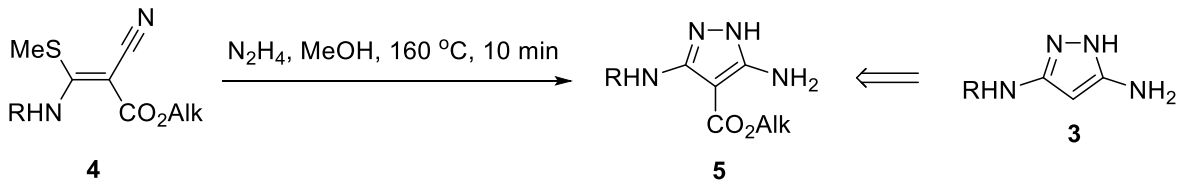


Figure 1. Selected bioactive 3,5-diaminopyrazoles.

2 Results and discussion

2.1 Synthesis of 3-amino-substituted 5-aminopyrazoles (3)

For the synthesis of 3-amino-substituted 5-aminopyrazoles **3** we decided to employ readily accessible 3-amino-substituted 5-aminopyrazole-4-carboxylates **5**, which can be conveniently prepared in good yields from 2-cyano-3-methylthioacrylates **4** using the previously described method (Scheme 1).[10] The hydrolytic decarboxylation of **5** was suggested as a potential route to 3-amino-substituted 5-aminopyrazoles **3**.



Scheme 1.

The initial optimization of reaction conditions for the synthesis **3** was performed using ethyl 5-amino-3-phenylaminopyrazole-4-carboxylate (**5a**) (Table 1). The reaction proceeded under microwave irradiation to form product **3a** in 2 mL of 2M aqueous solution of NaOH at 150 °C for 30 sec (Entry 1). Increasing the time of reaction (Entries 1-6) led to the further improvement of yields with the yield of 81% achieved at 150 °C in 4 min (Entry 5). Altering the concentration of NaOH did not led to an improvement in isolated yields (Entries 7 and 8). Conducting the reaction in 2M aqueous solution of K_2CO_3 or Na_2CO_3 led to lower yields (Entries 9 and 10), while changing the base to an acid (Entry 11) resulted in the isolation of the starting material **5a** only.

It should be noted that attempts to carry out the reaction under reflux for 12 h using 2M NaOH solution did not lead to the isolation of **3a** but rather to the recovery of starting material **5a**. However, an attempt to carry out the decarboxylation reaction of **5a** in 2M NaOH, imitating the optimised microwave irradiation conditions in the Monowave 50 reactor (Anton Paar), using sealed vessels under fast conventional heating successfully led

to the formation of equally pure **3a** in 75% yield. Therefore, there was minimal (if any) contribution of non-thermal microwave effects in promoting this reaction.

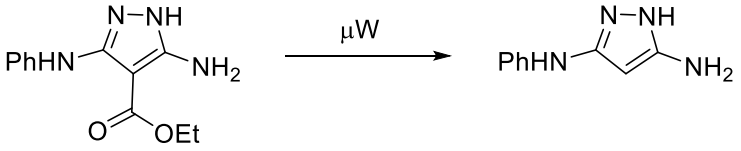
With the optimized conditions in hand, we decided to explore the scope of the reaction with a diverse library of 3-amino-substituted 5-aminopyrazole-4-carboxylates (**5**) as substrates. Compounds **5** were prepared according to the recently developed microwave-assisted approach.[10] Subsequently, the base-catalysed decarboxylation of ethyl 5-aminopyrazole-4-carboxylates **5** under microwave irradiation was found to proceed efficiently with the formation of desired products **3a**-**3l** in yields up to 85% (Table 2). A variety of arylamino and arylalkylamino substituents on the pyrazole ring was well tolerated with exclusive formation of compounds **3**, which were isolated in high purity *via* simple filtration. Using optimized conditions, we also attempted to carry out this reaction with methyl 3,5-diaminopyrazole-4-carboxylates **5**. For comparison purposes, **3a**, **3h** and **3j** were successfully prepared from the corresponding methyl esters **5**. In all cases, the hydrolytic decarboxylation of methyl and ethyl esters was efficiently performed in both 0.325 mmol and 3.25 mmol scales with similar outcomes (Table 2).

The structure assignments for the prepared 3,5-diaminopyrazoles **3** were made based on their spectral data. When compared with the spectra of reported staring materials,[10] we observed the disappearance of the characteristic ^{1}H NMR and ^{13}C NMR signals of the ethoxycarbonyl and methoxycarbonyl groups in addition to the absence of a C=O band in the IR spectra. Additionally, a signal assigned to H-4 atom of the pyrazole ring appeared in ^{1}H NMR spectra of **3** at 4.62-5.07 ppm.

Annular prototropic tautomerism is an interesting phenomenon, which has been widely investigated in aminopyrazoles.[11] In the ^{1}H NMR spectra of the prepared compounds, signals of protons of the exocyclic amino groups, C-H proton on the pyrazole ring and aromatic ring protons of 5-amino-3-arylaminopyrazoles **3a**-**3k** adjacent to the pyrazole ring appeared as broad signals. However, the tautomeric transformations were probably too fast to be detected on the ^{1}H NMR time-scale under the experimental conditions and therefore the tautomers were indistinguishable. For the compound **3l**, two tautomeric forms (K_T = 1.3) were detected in the NMR spectra in DMSO solution with 1*H*-form of 5-amino-3-phenethylaminopyrazole (**3l**) being predominant. Further study of the tautomeric preferences was performed on pyrazoles **3g** and **3i** using X-ray crystallography. While to a

first approximation the molecular structures of **3g** and **3i** appeared to be similar, crucially the compounds crystallized in the form of different tautomers as discussed in detail below.

Table 1. Optimization conditions for the synthesis of 5-amino-3-phenylaminopyrazole (**3a**)[a]



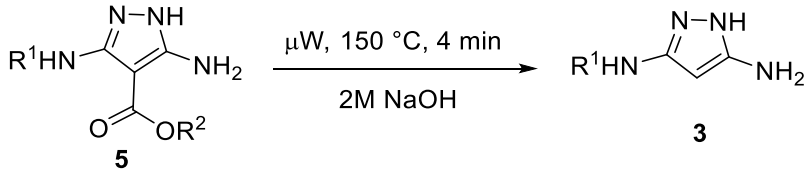
5a **3a**

Entry	Base/Acid	Temperature (°C)	Time (min)	Isolated yield (%)
1	2M NaOH	150	0.5	43
2	2M NaOH	150	1	40
3	2M NaOH	150	2	76
4	2M NaOH	150	3	80
5	2M NaOH	150	4	81
6	2M NaOH	150	5	72
7	1M NaOH	150	4	71
8	3M NaOH	150	4	64
9	2M K_2CO_3	150	4	25
10	2M Na_2CO_3	150	4	30
11	2M HCl	150	4	0[b]

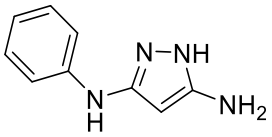
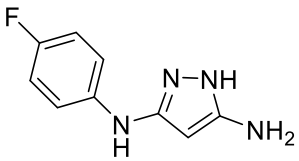
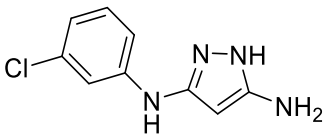
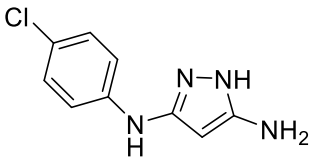
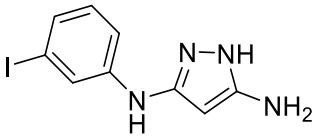
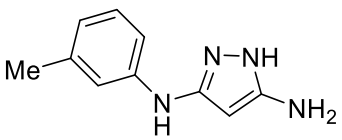
[a] The reaction was performed using a Discover SP CEM microwave synthesizer with 0.325 mmol of **5a** in 2 mL of the specified base or acid.

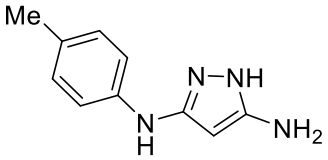
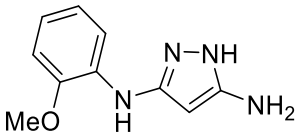
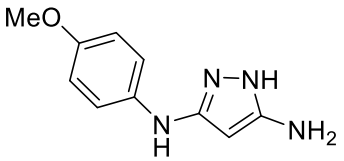
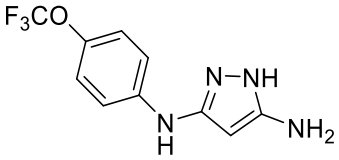
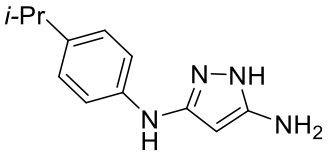
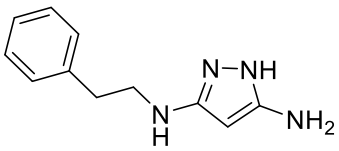
[b] Only starting material **5a** was isolated.

Table 2. Synthesis of 3-amino-substituted 5-aminopyrazoles (**3**) from 3,5-diaminopyrazole-4-carboxylates (**5**)[a]



5 **3**

Compound	Structure	Yield (%)		Mp (°C)
		0.325 mmol scale	3.25 mmol scale	
3a		81 74[b]	68 83[b]	166-168[c] Lit.:[6] 166
3b		61	68	165-167[c]
3c		60	47	58-60[c]
3d		69	57	169-171[d]
3e		63	55	138-140[d]
3f		42	55	111-112[d]

3g		70	79	166-167[c] Lit.:[6] 167-168
3h		44 40[b]	55 57[b]	111-112[e]
3i		78	70	164-166[c]
3j		69 81[b]	65 84[b]	107-108[d]
3k		85	88	186-187[f]
3l		71	60	135-136[d]

[a] The reactions were performed using a Discover SP CEM microwave synthesizer with 0.325 mmol or 3.25 mmol of ethyl 5-aminopyrazole-4-carboxylates **5** (R^2 = Et) in 2.0 mL or 20 mL of aqueous 2M NaOH at 150 °C for 4 min.

[b] The reaction was performed using a Discover SP CEM microwave synthesizer with 0.325 mmol or 3.25 mmol of methyl 5-aminopyrazole-4-carboxylates **5** (R^2 = Me) in 2.0 mL or 20 mL of aqueous 2M NaOH at 150 °C for 4 min.

Recrystallization solvents: [c] MeOH, [d] PhMe, [e] DMF & H_2O, [f] MeCN

2.2 X-ray crystallography of 5-amino-3-arylaminopyrazoles 3g and 3i

The crystallographic asymmetric unit of **3g** comprises two independent molecules, as shown in Figs. 2(a) and (b). The pyrazole ring is planar exhibiting a r.m.s. deviation for the fitted atoms of 0.0021 Å [0.0044 Å for the second independent molecule]. The appended primary-N3 and secondary-N5 amine atoms lie 0.073(3) and 0.072(3) Å out of and to the same side of the plane through the pyrazole ring [0.067(3) and 0.096(3) Å]. Twists in the molecule are noted as seen in the N1–C5–N5–C51 torsion angle of -155.09(16) [-144.91(16)°] and manifested in dihedral angles between the rings of 30.89(8) *cf*. 37.45(7)° indicating an inclined relationship, see Fig. 2(c) for an overlay diagram of the two independent molecules.

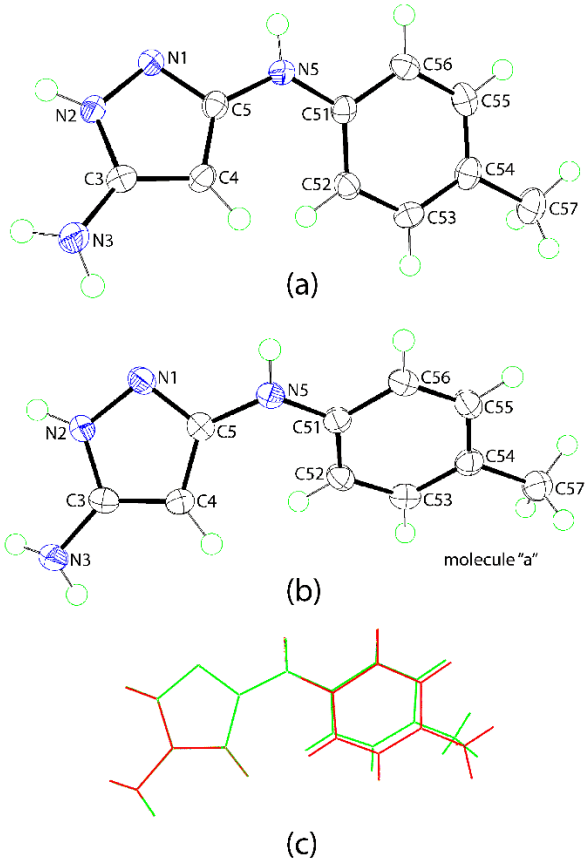


Figure 2. (a) and (b) The molecular structures of the first and second independent molecules comprising the asymmetric unit of **3g**, respectively, showing atom labelling scheme and 70% anisotropic displacement parameters, and (c) an overlay diagram of the two independent molecules: red image, the molecule shown in (a) and green image, molecule in (b). The molecules are overlapped so that the pyrazole rings are coincident.

Quite similar molecular features as described for **3g** are also evident in the structure of **3i**. Here, four independent molecules comprise the crystallographic asymmetric unit. The first of these is illustrated in Fig. 3(a) and the remainder, *i.e*. molecules "a", "b" and "c", in ESI Fig. S1[†]. As for **3g**, the pyrazole ring is planar [r.m.s. deviations for the fitted atoms of 0.0037, 0.0059, 0.0040 and 0.0049 Å for the four independent molecules, respectively]. Differences between the molecules occurs in the relationships between appended primary-N3 and secondary-N5 amine atoms to the pyrazole ring, lying to the opposite sides of the plane for the molecule shown in Fig. 3(a), *i.e*. 0.131(2) and 0.076(2) Å, and molecule "b" [0.125(2) and 0.074(2) Å], but, to the same side of the plane for molecules "a" [0.178(2) and 0.058(2) Å] and "c" [0.171(2) and 0.056(2) Å]. The rings are inclined with respect to each other, forming dihedral angles of 50.22(5), 44.38(5), 50.35(5) and 44.29(5)°, respectively. Finally, the methoxy group is close to co-planar to the ring it is connected in two molecules while slightly twisted in the other two [C57–O1–C54–C53 torsion angles: -4.0(2), 9.7(2), -4.0(2) and 9.8(2)°, respectively]. The disparity in the dihedral angles between the rings and in the relative orientations of the methoxy groups are highlighted in the overlay diagram of the four independent molecules shown in Fig. 3(b).

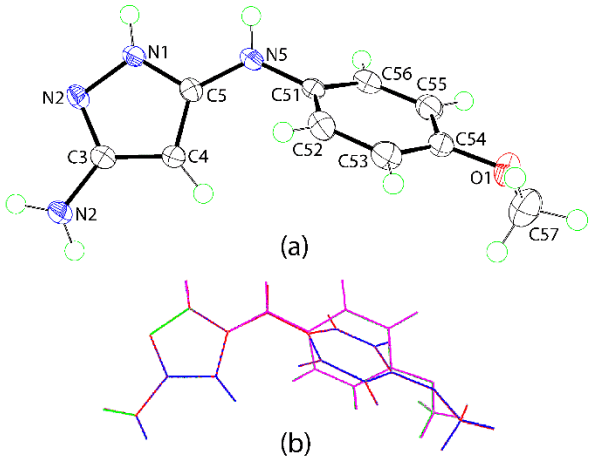


Figure 3. (a) The molecular structure of the first independent molecule of **3i** showing atom labelling scheme and 70% anisotropic displacement parameters and (b) an overlay diagram of the four independent molecules comprising the asymmetric unit of **3i**: red image, the molecule shown in (c), green image, molecule "a", blue, molecule "b" and pink, molecule "c". The molecules in are overlapped so that the pyrazole rings are coincident.

As indicated above, the key differences between the structures of **3g** and **3i** rests in the adopted tautomeric form, with **3g** being in the 3-*N*-(4-methylphenyl)-1*H*-pyrazole-3,5-diamine form while **3i** is in the 3-*N*-(4-methoxyphenyl)-2*H*-pyrazole-3,5-diamine form corresponding to the ring-nitrogen atoms being protonated at the N2 and N1 sites, respectively. As anticipated, the different tautomers give rise to systematic differences in the geometric parameters characterising the ring. Before detailing these, it is noted that only parameters for the molecules shown in Figs. 2(a) and 3(a) are discussed as for each structure, the parameters describing the other molecules comprising the asymmetric units are equal within experimental error to these, respectively. In terms of bond lengths within the rings, the reorganisation of π-electron density giving rise to the different tautomers results in a decrease [1.345(2) *cf*. 1.3314(19) Å], increase [1.383(2) *cf*. 1.404(2) Å] and decrease [1.405(2) *cf*. 1.389(2) Å] in the N2–C3, C3–C4 and C4–C5 bonds, respectively. In terms of bond angles, the values of the N2–N1–C5 [103.46(13) *cf*. 111.84(11)°] and N1–N2–C3 [111.99(14) *cf*. 103.70(11)°] follow the trends expected for protonated ring nitrogen atoms. The patterns noted in the molecular packing of **3g** and **3i** also confirm the assignments of the tautomeric forms of the five-membered rings.

The molecular packing of **3g** is replete with N–H···N hydrogen bonding that results in the formation of a supramolecular layer; geometric details of the intermolecular interactions are given in ESI Table S1†. Importantly and confirming the assignment of the 1*H*-pyrazole tautomer, the pyrazole-N2 atom functions as a donor and the adjacent N1 atom behaves as an acceptor for each molecule comprising the asymmetric unit. The independent molecules in **3g** have distinctive hydrogen bonding patterns and there are extensive interactions between the independent molecules. This point is illustrated by the bifurcated hydrogen bonds formed by the pyrazole-N2–H atoms which interact with two pyrazole-N1a atoms of two different (and independent) molecules in contrast to the pyrazole-N2a-H atoms which form hydrogen bonds with each of the pyrazole-N1 and N2 atoms of the same molecule; these pairs of contacts are indicated by "*i*" and "*ii*" in Fig. 4(a), respectively. The amine-N3/N3a–H atoms form hydrogen bonds with the pyrazole-N1a/N1 atoms of the other independent molecules and are indicated with "*iii*" and "*iv*" in Fig. 4(a). The aforementioned hydrogen bonds serve to link molecules into a helical chain propagating along the *b*-axis. The chains are assembled into a two-dimensional array

parallel to (1 0 1) *via* interactions involving amine-N3/N3a-H atoms as the donors. The amine-N3–H atoms form hydrogen bonds with the pyrazole-N2a and amine-N3a atoms of different molecules, shown as "*v*" and "*vi*". By contrast, the amine-N3a–H atoms do not form conventional hydrogen bonds with one of these participating in an amine-N3a–H···π(phenyl) interaction with the first independent molecule, indicated by "*vii*" in Fig. 4(a) and shown in detail in Fig. 4(b), whereas the second amine-N3a–H atom is separated 2.70 Å from the amine-N3 atom. Side-on and plan views of the supramolecular layer are shown in Fig. 4(c) and (d). The most obvious contacts between the layers to consolidate the three-dimensional packing are methyl-C57–H···π(C51a-C56a) interactions as highlighted in the unit cell diagram of ESI Fig. S2† from which it can be seen the phenyl groups project to either side of the layer.

Despite there being four independent molecules in the crystal of **3i**, to a first approximation the pattern of hydrogen bonding is relatively simple to describe; geometric details of the intermolecular interactions are given in ESI Table S2†. Thus, for each molecule, the pyrazole-N1–H forms a hydrogen bond to a pyrazole-N2 atom (thereby, confirming the 2*H*-pyrazole tautomer) as does one of the two amine-N3–H atoms so that each pyrazole-N2 accepts two hydrogen bonds. The amine-N5–H atom of each molecule forms a hydrogen bond to the amine-N3 atom. Some variation occurs for the second hydrogen atom of the amine-N3, being linked to amine-N5 in the cases of the molecule illustrated in Fig. 3(a) and molecule "b". For molecules "a" and "c", this atom participates in an amine-N3a–H···π(pyrazole) interaction. With the exception of the amine-N3b–H···N2b(pyrazole) hydrogen bond, all connections occur between different independent molecules. As for **3g**, all of the hydrogen bonding in the crystal of **3i** is focussed in specific regions of the crystal and lead to the formation of a supramolecular layers parallel to (1 1 0), as illustrated in Fig. 5. The phenyl groups project to either side of the layer and interact *via* phenyl-C–H···π(phenyl) interactions. Layers stack along the *c*-axis and are separated by hydrophobic interactions; the closest O···H contact between layers (2.88 Å) is well beyond the sum of their van der Waals radii (2.72 Å). A view of the unit cell contents is shown in ESI Fig. S3†.

It should be noted that the intermolecular interactions in crystals are critical for the stabilisation of the observed tautomeric forms; therefore, these preferences cannot be directly extrapolated to tautomeric equilibria in solutions.

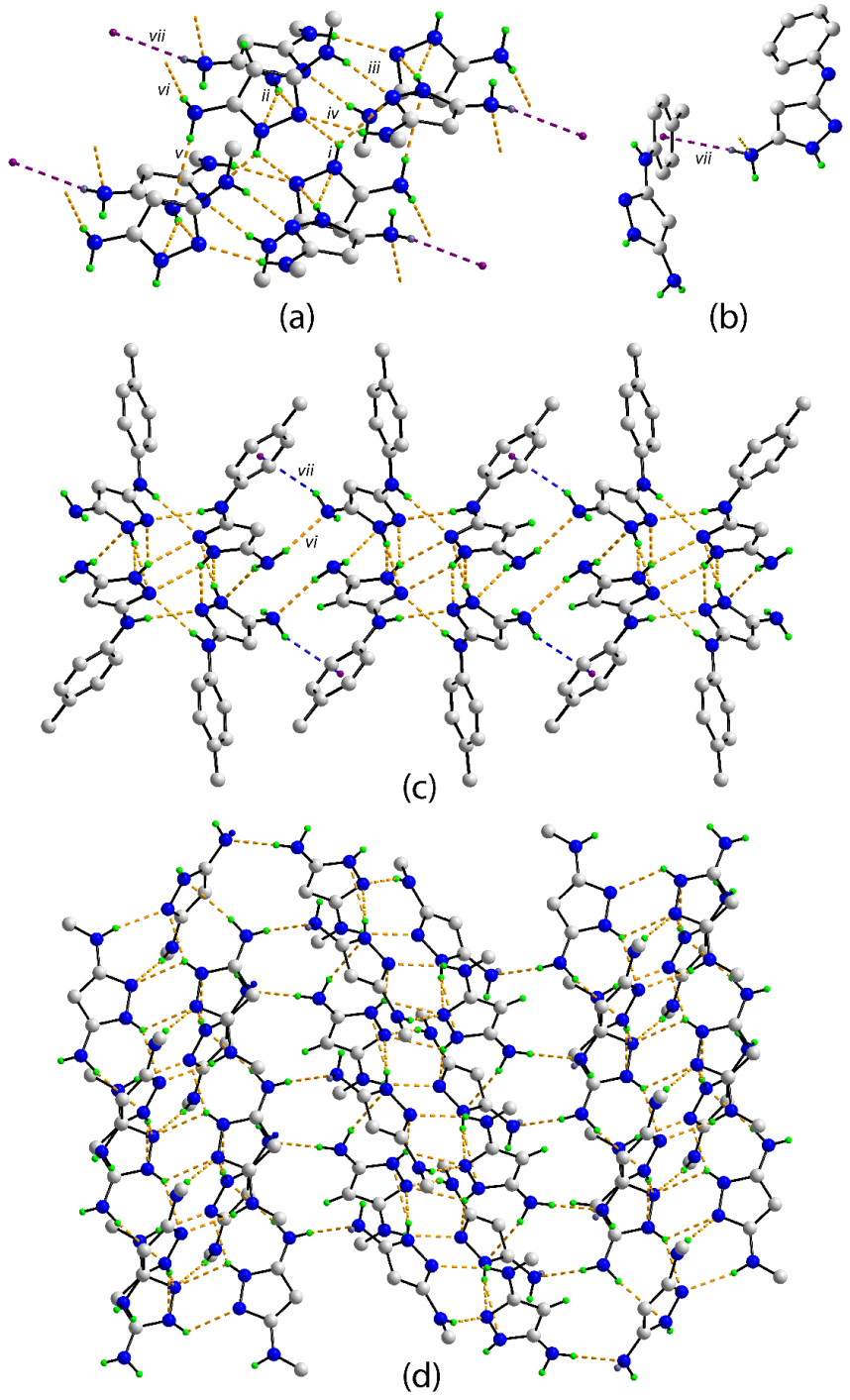


Figure 4. Supramolecular association in the crystal of **3g**: (a) N–H···N hydrogen bonding (see ESI Fig. S2 and Table S1[†]) leading to a supramolecular chain aligned along the *b*-axis, (b) detail of the amine-N3a–H···π(phenyl) interaction, (c) a side-on view of the supramolecular layer parallel to (1 0 1) and (d) a plan view of the layer (amine-N3a–H···π(phenyl) interactions are not shown). Please refer to the text for an explanation of "*i*"-"vii" in (a)-(c). In all

images, non-participating hydrogen atoms have been removed and in (a) and (d), only the *ipso*-carbon atom of the phenyl rings are shown.

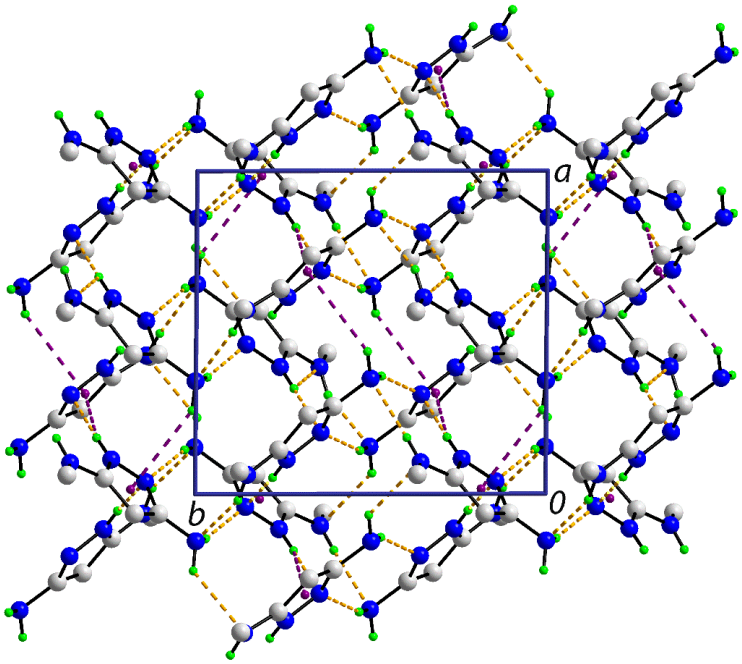


Figure 5. Supramolecular association in the crystal of **3i**: a view of the supramolecular layer parallel to (1 1 0). The N–H···N hydrogen bonding and N–H···π(pyrazole) interactions (see ESI Fig. S3 and Table S2[†]) are shown as orange and blue dashed lines, respectively. Only acidic hydrogen atoms and *ipso*-carbon atoms of the phenyl groups are shown.

3. Conclusion

A new efficient method for the synthesis of 3(5)-amino-substituted 5(3)-aminopyrazoles **3** was developed using hydrolytic decarboxylation of the ester group on the corresponding 3,5-diaminopyrazole-4-carboxylates **5** under microwave irradiation. The method was proven to be practical due to operational simplicity, short reaction time, good reproducibility and scalability. The X-ray crystallography performed on two representative aminopyrazoles **3g** and **3i** identified, on the basis of crystallographic refinement, systematic variations of key geometric parameters and intermolecular interactions, the presence of two different tautomers: the 1*H*- and 2*H*-pyrazole, respectively.

4. Experimental

4.1 General information

Melting points (uncorrected) were determined on a Stuart™ SMP40 automatic melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Fourier NMR spectrometer (300 MHz) using DMSO-d_6 as a solvent and TMS as an internal reference. IR spectra were recorded in KBr pellets using a Varian 640-IR spectrophotometer. Microwave-assisted reactions were carried out in the closed vessel focused single mode using a Discover SP microwave synthesizer (CEM, USA) monitoring reaction temperature by the equipped IR sensor. For the method validation, the model reaction was also carried out using Monowave 400 and Monowave 50 (Anton Paar, Austria) reactors.

*4.2 General method for the microwave-assisted synthesis of 3-amino-substituted 5-aminopyrazoles **3***

An ethyl 3,5-diaminopyrazole-4-carboxylate (**5**) (0.325 mmol) in 2M aqueous solution of NaOH (2.0 mL) was irradiated in a 10 mL seamless pressure vial using microwave system operating at maximal microwave power up to 150 W (Discover SP, CEM) at 150 °C for 4 min. After cooling, the precipitated product **3** was filtered and washed with cold water and recrystallised from a suitable solvent. The reaction was also replicated in an increase scale of ethyl 3,5-diaminopyrazole-4-carboxylates (**5**) (3.25 mmol) in aqueous 2M NaOH (20 mL). The same procedure was also effectively applied using the selected methyl 3,5-diaminopyrazole-4-carboxylates (**5**) as the starting material.

*4.2.1 5-Amino-3-phenylaminopyrazole (**3a**)*

Yield (0.325 / 3.25 mmol scale): 81% / 68% (74% / 76% from the methyl ester); mp 166-168 °C (MeOH), lit.:[6] 166 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.88-4.91 (3H, br s, NH_2 and H-4), 6.63 (1H, t, ^{3}J = 7.1 Hz, H-4'), 7.11 (2H, t, ^{3}J = 7.8 Hz, H-3' and H-5'), 7.29 (2H, d, ^{3}J = 6.0 Hz, H-2' and H-6'), 8.01 (1H, br s, NH), 10.47 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 77.2 (C-4), 114.7 (C-2' and C-6'), 117.2 (C-4'), 128.5 (C-3' and C-5'), 144.2 (C-1'), 147.9 (C-3), 151.1 (C-5). IR (KBr): ν 3359 (N-H), 3310 (N-H), 3148 (C-H), 1618, 1581, 1451, 1276, 1173,

1093, 1005 cm^{-1}. Anal. calcd. for $C_9H_{10}N_4$: C, 62.05; H, 5.8; N, 32.2. Found: C, 61.9; H, 6.0; N, 31.9.

*4.2.2 5-Amino-3-(4-fluorophenyl)aminopyrazole (**3b**)*

Yield (0.325 / 3.25 mmol scale): 61% / 68%; mp 165-167 °C (MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.88 (3H, br s, NH_2 and H-4), 6.95 (2H, dd, $^3J_{HH}$ = 8.9 Hz, $^2J_{HF}$ = 8.9 Hz, H-3′ and H-5′), 7.31 (2H, br s, H-2′ and H-6′), 8.04 (1H, br s, NH), 10.46 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 76.7 (C-4), 114.7 (d, $^2J_{CF}$ = 21.7 Hz, C-3′ and C-5′), 115.6 (d, $^3J_{CF}$ = 7.24 Hz, C-2′ and C-6′), 140.7 (d, $^4J_{CF}$ = 2.2 Hz, C-1′), 147.9 (C-3), 151.2 (C-5), 154.7 (d, $^1J_{CF}$ = 233.1 Hz, C-4′). IR (KBr): ν 3359 (N-H), 3312 (N-H), 3143 (C-H), 1624, 1586, 1502, 1278, 1238, 1101, 1005 cm^{-1}. Anal. calcd. for $C_9H_9FN_4$: C, 56.2; H, 4.7; N, 29.15. Found: C, 56.05; H, 4.9; N, 28.0.

*4.2.3 5-amino-3-(3-chlorophenyl)aminopyrazole (**3c**)*

Yield (0.325 / 3.25 mmol scale): 60% / 47%; mp 58-60 °C (MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.90-4.95 (3H, br s, NH_2 and H-4), 6.64-6.67 (1H, m, H-4′), 7.10-7.15 (2H, m, H-5′ and H-6′), 7.62 (1H, br s, H-2′), 8.36 (1H, br s, NH), 10.58 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 77.1 (C-4), 113.3 (C-6′), 113.8 (C-2′), 116.5 (C-4′), 129.8 (C-5′), 133.1 (C-3′), 145.4 (C-1′), 147.9 (C-3), 150.5 (C-5). IR (KBr): ν 3359 (N-H), 3288 (N-H), 3143 (C-H), 1630, 1585, 1483, 1422, 1257, 1093, 1010 cm^{-1}. Anal. calcd. for $C_9H_9ClN_4$: C, 51.8; H, 4.35; N, 26.85. Found: C, 51.7; H, 4.5; N, 26.7.

*4.2.4 5-Amino-3-(4-chlorophenyl)aminopyrazole (**3d**)*

Yield (0.325 / 3.25 mmol scale): 69% / 57%; mp 169-171 °C (PhMe); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.89-4.91 (3H, br s, NH_2 and H-4), 7.14 (2H, d, ^3J = 8.8 Hz, H-3′ and H-5′), 7.34 (2H, d, ^3J = 7.4 Hz, H-2′ and H-6′), 8.24 (1H, br s, NH), 10.53 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 77.0 (C-4), 116.0 (C-2′ and C-6′), 120.3 (C-4′), 128.1 (C-3′ and C-5′), 142.9 (C-1′), 147.9 (C-3), 150.7 (C-5). IR (KBr): ν 3453 (N-H), 3367 (N-H), 3282 (C-H), 1623, 1595, 1548, 1472, 1249, 1177, 1088 cm^{-1}. Anal. calcd. for $C_9H_9ClN_4$: C, 51.8; H, 4.35; N, 26.85. Found: C, 51.6; H, 4.5; N, 26.6.

*4.2.5 5-Amino-3-(3-iodophenyl)aminopyrazole (**3e**)*

Yield (0.325 / 3.25 mmol scale): 63% / 55%; mp 138-140 °C (PhMe); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.89-4.93 (3H, br s, NH_2 and H-4), 6.87-6.92 (1H, m, H-5′), 6.95-6.99 (1H, m, H-

4'), 7.16 (1H, d, ^{3}J = 6.8 Hz, H-6'), 7.90 (1H, br s, H-2'), 8.25 (1H, br s, NH), 10.57 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 77.1 (C-4), 94.9 (C-3'), 114.1 (C-6'), 122.5 (C-2'), 125.5 (C-4'), 130.4 (C-5'), 145.4 (C-1'), 147.9 (C-3), 150.4 (C-5). IR (KBr): ν 3383 (N-H), 3304 (N-H), 3160 (C-H), 1573, 1475, 1395, 1269, 1166, 1095, 1063 cm^{-1}. Anal. calcd. for $C_9H_9IN_4$: C, 36.0; H, 3.0; N, 18.7. Found: C, 35.9; H, 3.2; N, 18.5.

*4.2.6 5-Amino-3-(3-methylphenyl)aminopyrazole (**3f**)*

Yield (0.325 / 3.25 mmol scale): 42% / 55%; mp 111-112 °C (PhMe); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.20 (3H, s, CH_3), 4.86-4.91 (3H, br s, NH_2 and H-4), 6.46 (1H, d, ^{3}J = 6.8 Hz, H-4'), 6.96-7.13 (3H, m, H-2', H-5' and H-6'), 7.92 (1H, br s, NH), 10.46 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.3 (CH_3), 77.2 (C-4), 111.9 (C-6'), 115.1 (C-2'), 118.1 (C-4'), 128.3 (C-5'), 137.3 (C-3'), 144.1 (C-1'), 147.8 (C-3), 151.2 (C-5). IR (KBr): ν 3400 (N-H), 3302 (N-H), 3235 (C-H), 1581, 1493, 1435, 1282, 1165, 1071, 1000 cm^{-1}. Anal. calcd. for $C_{10}H_{12}N_4$: C, 63.8; H, 6.4; N, 29.8. Found: C, 63.65; H, 6.6; N, 29.6.

*4.2.7 5-Amino-3-(4-methylphenyl)aminopyrazole (**3g**)*

Yield (0.325 / 3.25 mmol scale): 70% / 79%; mp 166-167 °C (MeOH), lit.:[6] 167-168 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.17 (3H, s, CH_3), 4.86 (3H, br s, NH_2 and H-4), 6.92 (2H, d, ^{3}J = 8.3 Hz, H-3' and H-5'), 7.19 (2H, br s, H-2' and H-6'), 7.86 (1H, br s, NH), 10.41 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.1 (CH_3), 76.9 (C-4), 114.7 (C-2' and C-6'), 125.5 (C-4'), 128.8 (C-3' and C-5'), 141.7 (C-1'), 147.8 (C-3), 151.4 (C-5). IR (KBr): ν 3399 (N-H), 3319 (N-H), 3189 (C-H), 1616, 1580, 1514, 1298, 1180, 1180, 1100 cm^{-1}. Anal. calcd. for $C_{10}H_{12}N_4$: C, 63.8; H, 6.4; N, 29.8. Found: C, 63.7; H, 6.6; N, 29.6.

*4.2.8 5-Amino-3-(2-methoxyphenyl)aminopyrazole (**3h**)*

Yield (0.325 / 3.25 mmol scale): 44% / 55% (40% / 57% from methyl 5-aminopyrazole-4-carboxylate); mp 111-112 °C (DMF &H_2O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.82 (3H, s, OCH_3), 4.89 (2H, br s, NH_2), 5.07 (1H, br s, H-4), 6.67 (1H, t, ^{3}J = 7.3 Hz , H-5'), 6.79 (1H, t, ^{3}J = 7.3 Hz, H-4'), 6.87 (1H, d, ^{3}J = 7.7 Hz, H-3'), 6.99 (1H, br s, NH), 7.92 (1H, d, ^{3}J = 7.9 Hz, H-6'), 10.51 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.4 (OCH_3), 77.7 (C-4), 109.9 (C-3'), 114.0 (C-6'), 117.4 (C-4'), 120.6 (C-5'), 132.9 (C-1'), 146.1 (C-2'), 147.8 (C-3), 150.8 (C-5). IR

(KBr): ν 3423 (N-H), 3339 (N-H), 3310 (C-H), 1600, 1578, 1460, 1296, 1251, 1114, 1023 cm^{-1}. Anal. calcd. for $C_{10}H_{12}N_4O$: C, 58.8; H, 5.9; N, 27.4. Found: C, 58.7; H, 6.1; N, 27.3.

*4.2.9 5-Amino-3-(4-methoxyphenyl)aminopyrazole (**3i**)*

Yield (0.325 / 3.25 mmol scale): 78% / 70%; mp 164-166 °C (MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.69 (3H, s, OCH_3), 4.85 (3H, br s, NH_2 and H-4), 6.74 (2H, d, ^3J = 8.8 Hz, H-3′ and H-5′), 7.24 (2H, d, ^3J = 7.4 Hz, H-2′ and H-6′), 7.74 (1H, br s, NH), 10.36 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.1 (OCH_3), 76.5 (C-4), 113.9 (C-3′ and C-5′), 115.9 (C-2′ and C-6′), 138.0 (C-1′), 147.8 (C-3), 151.4 (C-5), 151.7 (C-4′). IR (KBr): ν 3395 (N-H), 3288 (N-H), 3148 (C-H), 1609, 1583, 1442, 1248, 1178, 1108, 1036 cm^{-1}. Anal. calcd. for $C_{10}H_{12}N_4O$: C, 58.8; H, 5.9; N, 27.4. Found: C, 58.7; H, 6.1; N, 27.2.

*4.2.10 5-Amino-3-(4-trifluoromethoxyphenyl)aminopyrazole (**3j**)*

Yield (0.325 / 3.25 mmol scale): 69% / 65% (81% / 84% from methyl 5-aminopyrazole-4-carboxylate); mp 107-108 °C (PhMe); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.91 (3H, br s, NH_2 and H-4), 7.11 (2H, d, ^3J = 8.6 Hz, H-3′ and H-5′), 7.38 (2H, d, ^3J = 7.1, H-2′ and H-6′), 8.31 (1H, br s, NH), 10.55 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 77.0 (C-4), 115.4 (C-2′ and C-6′), 120.3 (q, $^1J_{CF}$ = 250.6 Hz, CF_3), 121.5 (C-3′ and C-5′), 139.3 (q, $^3J_{CF}$ = 2.5 Hz, C-4′), 143.4 (C-1′), 147.9 (C-3), 150.7 (C-5). IR (KBr): ν 3400 (N-H), 3295 (N-H), 3209 (C-H), 1583, 1513, 1324, 1219, 1175, 1003 cm^{-1}. Anal. calcd. for $C_{10}H_9F_3N_4O$: C, 46.5; H, 3.5; N, 21.7. Found: C, 46.4; H, 3.6; N, 21.6.

*4.2.11 5-Amino-3-(4-isopropylphenyl)aminopyrazole (**3k**)*

Yield (0.325 / 3.25 mmol scale): 85% / 88%; mp 186-187 °C (MeCN); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15 (6H, d, ^3J = 6.9 Hz , $(CH_3)_2$), 2.75 (1H, m, ^3J = 6.9 Hz , CH), 4.85-4.89 (3H, br s, NH_2 and H-4), 6.99 (2H, d, ^3J = 8.5 Hz, H-3′ and H-5′), 7.17 (2H, d, ^3J = 7.4 Hz, H-2′ and H-6′), 7.86 (1H, br s, NH), 10.43 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.1 (2 x CH_3), 32.49 (CH), 76.90 (C-4), 114.7 (C-2′ and C-6′), 126.1 (C-3′ and C-5′), 137.0 (C-4′), 142.0 (C-1′), 147.8 (C-3), 151.4 (C-5). IR (KBr): ν 3395 (N-H), 3312 (N-H), 2957 (C-H), 1618, 1597, 1552, 1289, 1187, 1187, 1103 cm^{-1}. Anal. calcd. for $C_{12}H_{16}N_4$: C, 66.6; H, 7.5; N, 25.9. Found: C, 66.5; H, 7.5; N, 25.8.

*4.2.12 5-Amino-3-phenethylaminopyrazole (**3l**)*

Yield (0.325 / 3.25 mmol scale): 71% / 60%; mp 135-136 °C (PhMe); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.77 (2H, t, ^{3}J = 7.4 Hz, CH_2), 3.14 (2H, q, ^{3}J = 7.0 Hz, CH_2), 4.15* and 4.69 (2H, br s, NH_2), 4.62 (1H, s, H-4), 4.69 and 5.14* (1H, br s, NH), 7.12-7.33 (5H, m, Ph), 10.02 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.6 (CH_2), 45.6 (CH_2), 74.7 (C-4), 125.7 (C-4'), 128.1 (C-2' and C-6'), 128.5 (C-3' and C-5'), 139.8* and 140.3 (C-1'), 148.3 and 150.0* (C-3), 154.9* and 156.3 (C-5); * - signals of the minor tautomer. IR (KBr): ν 3382 (N-H), 3303 (N-H), 3243 (C-H), 1590, 1559, 1499, 1371, 1187, 1099, 1061 cm^{-1}. Anal. calcd. for $C_{11}H_{14}N_4$: C, 65.3; H, 7.0; N, 27.7. Found: C, 65.2; H, 7.2; N, 27.45.

*4.3 Synthesis of 5-amino-3-phenylaminopyrazole (**3a**) via heating in a sealed vessel.*

An ethyl 5-amino-3-phenylaminopyrazole-4-carboxylate (**5a**, 80 mg, 0.325 mmol) in 2M aqueous solution of NaOH (2 mL) was heated in a 10 mL seamless pressure vial in an enclosed system (Monowave 50, Anton Paar) at 150 °C for 4 min. After cooling, the precipitate was filtered to obtain a compound, which was identical to **3a** prepared under microwave irradiation. Yield 75%.

4.4 X-ray crystallographic analysis

Intensity data for **3g** and **3i** were measured for colourless crystals (**3g**: 0.03 x 0.12 x 0.23 mm; **3i**: 0.04 x 0.11 x 0.21 mm) at 100 K on an Rigaku/Oxford Diffraction XtaLAB Synergy diffractometer (Dualflex, AtlasS2) fitted with CuKα radiation (λ = 1.54178 Å) so that θ_{max} = 67.1°. Data reduction and Gaussian absorption corrections were by standard methods.[12] The structures were solved by direct methods[13] and refined[14] on F^2 with anisotropic displacement parameters and C-bound H atoms included in the riding model approximation. The N-bound H atoms were refined freely. A weighting scheme of the form $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$) was introduced in each case. In the refinement of **3g**, two reflections, *i.e*. (2 0 4) and (3 0 1), were removed from the final cycles of refinement owing to poor agreement. The molecular structure diagrams showing 70% probability displacement ellipsoids were generated by ORTEP for Windows[15] and the packing diagrams with DIAMOND.[16] Additional data analysis was made with PLATON.[17]

*4.4.1 Crystal data for **3g**:* $C_{10}H_{12}N_4$, *M* = 188.24, monoclinic, $P2_1/n$, *a* = 18.0137(5), *b* = 6.15230(10), *c* = 18.2375(5) Å, β = 114.056(3)°, *V* = 1845.64(9) Å^3, *Z* = 8, D_x = 1.355 g cm^{-3}, *F*(000) = 800, μ = 0.693 mm^{-1}, no. reflns meas. = 23354, no. unique reflns = 3290 (R_{int} = 0.047), no. reflns with $I \geq 2\sigma(I)$ = 2949, no. parameters = 287, *R*(obs. data) = 0.045, *a* and *b* in weighting scheme = 0.047 and 1.490, *wR*2(all data) = 0.111. CCDC deposition number: 1866662.

*4.4.2 Crystal data for **3i**:* $C_{10}H_{12}N_4O$, *M* = 204.24, triclinic, $P\bar{1}$, *a* = 9.6175(2), *b* = 10.4055(2), *c* = 20.1541(3) Å, α = 85.3860(10), β = 83.139(2), γ = 89.982(2)°, *V* = 1995.90(6) Å^3, *Z* = 8, D_x = 1.359 g cm^{-3}, *F*(000) = 864, μ = 0.763 mm^{-1}, no. reflns meas. = 46475, no. unique reflns = 7127 (R_{int} = 0.042), no. reflns with $I \geq 2\sigma(I)$ = 6104, no. parameters = 609, *R*(obs. data) = 0.046, *a* and *b* in weighting scheme = 0.095 and 0.536, *wR*2(all data) = 0.139. CCDC deposition number: 1866664.

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Appendix A. Supplementary data

† Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.tet.XXXX.XX.XXXX

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