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The conversion of isothiazoles into pyrazoles using hydrazine

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ABSTRACT

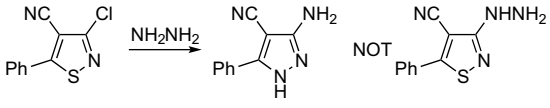
The conversion of isothiazoles into pyrazoles on treatment with hydrazine is investigated. The influence of various C-3, C-4 and C-5 isothiazole substituents and some limitations of this ring transformation are examined. When the isothiazole C-3 substituent is a good nucleofuge, 3-aminopyrazoles are obtained. However, when the 3-substituent is not a leaving group it is retained in the pyrazole product. Treatment of 4-bromo-3-chloro-5-phenylisothiazole **56** or 3-chloro-4,5-diphenylisothiazole **57** with anhydrous hydrazine at ca. 200 °C for a few minutes gives the corresponding 3-hydrazinoisothiazoles **61** and **64** respectively in high yields; the stability of these new hydrazines is investigated. 5,5′-Diphenyl-3,3′-biisothiazole-4,4′-dicarbonitrile **78** reacts with hydrazine to give 5,5′-diphenyl-3,3′-bi(1*H*-pyrazole)-4,4′-dicarbonitrile **79**. Methylhydrazine reacts with 3-chloro-5-phenylisothiazole-4-carbonitrile **1** to give 3-(1-methylhydrazino)-5-phenylisothiazole-4-carbonitrile **83** and 3-amino-1-methyl-5-phenylpyrazole-4-carbonitrile **84**. All products are fully characterised and rational mechanisms for the isothiazole into pyrazole transformation are proposed.

1. Introduction

Pyrazoles (1,2-diazoles) rarely occur in nature, however they are structural components of many biologically active compounds. Important commercial pyrazole products include Sildenafil (Viagra®),[1] Lonazolac,[2,3] Difenamizole,[4] Mepirizole,[5] Phenidone,[6] and bicyclic pyrazolidinone LY 186826.[7] Synthetic methods for the preparation of monocyclic pyrazoles are well documented[8–11] and a common synthetic strategy involves the reaction of 1,3-dicarbonyl compounds or their equivalents with hydrazine. Heterocycles that can behave as 1,3-dicarbonyl equivalents can therefore be transformed into pyrazoles on treatment with hydrazines.[11]

Recently we tried to prepare 3-hydrazino-5-phenylisothiazole-4-carbonitrile **3** from 3-chloro-5-phenylisothiazole-4-carbonitrile **1** using neat anhydrous hydrazine but obtained in quantitative yield 3-amino-5-phenylpyrazole-4-carbonitrile **2** (Scheme 1).[12] This pyrazole, first prepared by treating [2-methoxy(phenyl)methylene]-malononitrile with hydrazine monohydrate,[13] when in solution is in a dynamic solvent dependent prototropic equilibrium[14–17] with isomer 5-amino-3-phenylpyrazole-4-carbonitrile. No attempt to differentiate between prototropic isomers will be presented here.

The analogous transformation of isoxazoles into pyrazoles using arylhydrazines[18–34] or alkylhydrazines[35] is well documented. Furthermore the transformations of isoxazolium salts,[36] isoxazolidin-2-yl,[37] isoxazolidin-5-ones,[38] isoxazol-4-one oximes[39,40] and isoxazole-4,5-diones[41] into pyrazoles have been reported. While there are several reports on the analogous conversion of isothiazolium salts into pyrazoles,[42–45] there is only one report on the transformation of isothiazoles into pyrazoles using arylhydrazines.[46] We now report an extended study on the transformation of substituted isothiazoles into pyrazoles on treatment with hydrazine.



1 2 3

Scheme 1.

2. Results and discussion

In an early effort to avoid the need for excess neat anhydrous hydrazine, the use of hydrazine monohydrate with a co-solvent to improve solubility was studied (Table 1).

The use of either DMF or DMSO as co-solvent was satisfactory for the room temperature conversion of 3-chloro-5-phenylisothiazole-4-carbonitrile **1** into the pyrazole **2**, while the use of ethanol required heating to reflux owing to poor solubility of the starting isothiazole. Of the three co-solvents investigated, DMSO gave the cleanest reaction mixtures (by TLC), however, there remained a need for a large excess (>100 equiv) of hydrazine

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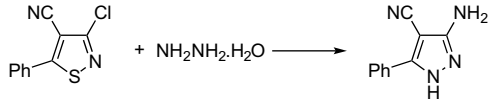
Table 1
Reaction of 3-chloro-5-phenylisothiazole-4-carbonitrile **1** (0.230 mmol) with $NH_2NH_2{\cdot}H_2O$ in different solvents (1 mL)



1 **2**

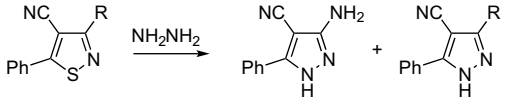
$NH_2NH_2{\cdot}H_2O$ (equiv)	Solvent	Temp (°C)	Time (h)	Yield **2** (%)
10	DMSO	20	5.5	50
15	DMSO	20	5	51
25	DMSO	20	1	65
100	DMSO	20	1	72
100	DMF	20	1	60
100	EtOH	20–80	1	87
150	DMSO	20	0.5	89
200	DMSO	20	0.5	92

monohydrate to obtain short reaction times and high product yields. By comparison neat anhydrous hydrazine gave the cleanest reaction mixtures and since the absence of a co-solvent also facilitated isolation of pyrazole product all further studies were conducted using neat anhydrous hydrazine.

2.1. Modification of substituents at C-3

A structural comparison of the pyrazole product and the starting isothiazole indicated that cleavage of the C–R bond at the isothiazole C-3 position must occur during the transformation. As such the leaving group ability of the C-3 substituent was investigated (Table 2). The reaction times of the 3-halo derivatives (**1** R=Cl, **4** R=Br, **5** R=I) decreased in accordance with the nucleofugality of the halide. However, when the C-3 substituent was methoxy, hydroxyl or alkylamino, which are by comparison poor nucleofuges, new major pyrazole products **12**–**15** were isolated that retained the C-3 substituent together with some of the 3-aminopyrazole **2**. The conversion of 3,5-diphenylisothiazole-4-carbonitrile **11**, which has no leaving group at C-3 (R=Ph), into 3,5-diphenylpyrazole-4-carbonitrile **16** (83%) required harsh conditions (150 °C, sealed tube).

Table 2
Reaction of 5-phenyl-3-substituted-isothiazole-4-carbonitrile **1**, **4**–**11** (0.230 mmol) with anhydrous hydrazine (2 mL) at ca. 20 °C

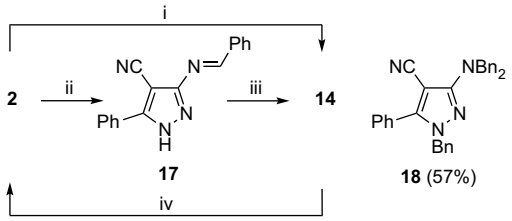


1, **4-11** **2** **12-16**

	R	Time (min)	Yields (%)	
			2	**12–16**
1	Cl	15	99	0
4	Br	10	100	0
5	I	5	98	0
6	MeO	15	48	**12** (52)
7	HO	30	3	**13** (97)
8	H_2N	20	93	—
9	BnNH	4.5 h	33	**14** (67)
10	*N*-Morpholino	36 h	55	**15** (40)
10	*N*-Morpholino	30 (80 °C)	44	**15** (56)
11	Ph	24 h (150 °C)[a]	0	**16** (83)

[a] Sealed tube.

Interestingly the major product of the reaction between 3-benzylamino-5-phenylisothiazole-4-carbonitrile **9** and hydrazine was 3-benzylamino-5-phenylpyrazole-4-carbonitrile **14** (67%). To the best of our knowledge the 3-benzylaminopyrazole **14** has not previously been reported and in our hands its preparation via direct regiocontroled N-benzylation of the 3-amino-5-phenylpyrazole-4-carbonitrile **2** using benzyl bromide and KOH, led to a complex mixture from which the desired product **14** could be isolated in low yield (33%) together with the tribenzylated pyrazole **18** (57%). Nevertheless a two step benzylation via the imine[47] **17** followed by treatment with $NaBH_4$ in MeOH gave the *N*-benzylaminopyrazole **14** in a good overall yield of 72% (Scheme 2).



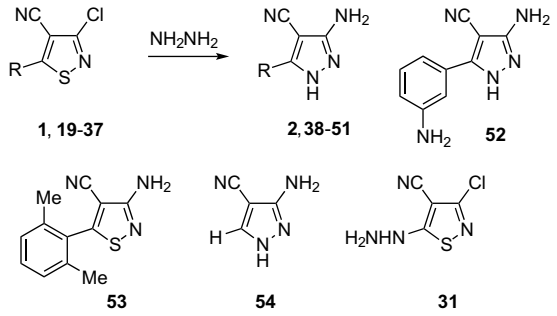
Scheme 2. Reagents and conditions: (i) $PhCH_2Br$ (1 equiv), KOH (12 equiv), DMF, 20 °C, 15 min, 33%; (ii) PhCHO (36 equiv=1 mL), 20 °C, 2 h, 72%; (iii) $NaBH_4$ (2 equiv), MeOH, 0–20 °C, Ar, 10 min, 100%; (iv) H_2O/MeOH (5%), 20 °C, 15 min, 99%.

2.2. Modification of substituents at C-5

The transformation of isothiazole into pyrazole required that C–N bond formation occurs at the isothiazole C-5 carbon. This carbon, known to be highly electrophilic,[48–50] was a probable site for initial attack by hydrazine and as such both steric and electronic factors that influence the C-5 position could affect the ring transformation. To investigate this, a series of 3-chloro-5-substituted isothiazole-4-carbonitriles bearing steric and/or electronic constraints at C-5 were treated with anhydrous hydrazine to examine their effect on reaction time and pyrazole yields (Table 3).

Electron rich aryl and thien-3-yl substituents at C-5 (e.g., isothiazoles **20**–**23**) led to long reaction times (1–4 h) while comparitively electron poor aryl substituents (e.g., isothiazoles **24**–**26**) led to short reaction times (15–30 min). More interestingly the isothiazole **28** bearing the sterically demanding 2,6-dimethylphenyl substituent at C-5 reacted slowly (8 h) with anhydrous hydrazine to give 3-amino-5-(2,6-dimethylphenyl)isothiazole-4-carbonitrile **53** in good yield (70%). Tentatively this 3-aminoisothiazole is derived from the 3-hydrazinyl derivative (see below, Tables 5–8), although all our efforts to isolate this were not successful. The data supported that the C-5 substituent influenced the reaction both sterically and electronically and tentatively supported that hydrazine initially attacked the isothiazole C-5 position. This was further supported when the C-5 substituent could act as a leaving group. Isothiazoles with poor leaving groups at C-5 such as the 5-morpholino, 5-anilino- and 5-benzylaminoisothiazoles **29**, **32** and **33** gave the expected morpholino, anilino and benzylamino substituted pyrazoles **47**, **49** and **50** respectively in good yield, however, where the C-5 isothiazole substituent was a better nucleofuge (e.g., PhO, PhS and Cl substituted isothiazoles **35**–**37**) only the 5-hydrazinylisothiazole **31** was obtained quickly and in good yield. Several examples of the replacement of leaving groups (e.g., halogen,[49,51,52] OEt,[53] SR,[51,54] and SO_2R,[55]) at the isothiazole C-5 position by hydrazine monohydrate are known and the displacement of phenoxy groups by hydrazine from heteroarenes, (e.g., from [1,2,4]dithiazolo-[1,5-*b*][1,2,4]dithiazoles,[56] acridines[57,58] and phthalazines[59]), has been previously reported. The data collected, suggested that the conversion of 5-amino-3-chloroisothiazole-4-carbo-nitrile **30** into 3,5-diaminopyrazole-4-carbonitrile **48** at ambient temperatures probably does not proceed via initial displacement of the C-5 amine by hydrazine to give the intermediate hydrazinylisothiazole **31**. Nevertheless under more forcing conditions (110 °C), a pure sample of 3-chloro-5-hydrazinylisothiazole-4-carbonitrile **31** treated with anhydrous

Table 3
Reaction of 3-chloro-5-substituted isothiazole-4-carbonitriles **1**, **19–37** (0.230 mmol) in anhydrous hydrazine (2 mL) at ca. 20 °C

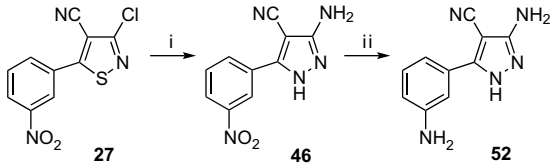


	R	Time (h)	Yields (%)	
			2, **38–51**	**31**, **52–54**
1	Ph	0.25	**2** (99)	—
19	3-MeC_6H_4	0.33	**38** (97)	—
20	2-$MeOC_6H_4$	3	**39** (95)	—
21	3-$MeOC_6H_4$	3–2.5	**40** (100)	—
22	4-$MeOC_6H_4$	4	**41** (94)	—
23	3-Thienyl	1	**42** (94)	—
24	2-ClC_6H_4	0.25	**43** (90)	—
25	3-ClC_6H_4	0.25	**44** (89)	—
26	4-ClC_6H_4	0.50	**45** (86)	—
27	3-$NO_2C_6H_4$	1	**46** (72)	**52** (28)
28	2,6-$(Me)_2C_6H_3$	8	—	**53** (70)
29	*N*-Morpholino	1	**47** (82)	—
30	NH_2	0.08	**48** (84)	—
31	$NHNH_2$	24	nr[a]	—
31	$NHNH_2$	0.75 (110 °C)	**48** (86)	**54** (13)
32	PhNH	24	nr[a]	—
32	PhNH	1 (110 °C)	**49** (91)	—
33	BnNH	24	nr[a]	—
33	BnNH	0.33 (110 °C)	**50** (92)	—
34	MeO	0.05	**51** (65)	**31** (30)
35	PhO	0.08	—	**31** (85)
36	PhS	0.08	—	**31** (90)
37	Cl	0.08	—	**31** (100)

[a] nr=no reaction.

hydrazine gave 3,5-diaminopyrazole-4-carbonitrile **48** (86%) together with some reduced 3-aminopyrazole-4-carbonitrile **54** (13%). Heating (ca. 200 °C) a pure sample of the 5-hydrazinylisothiazole **31** gave a very complex mixture (by TLC) which was not pursued further. Interestingly a colourless DMSO solution of pure 3-chloro-5-hydrazinylisothiazole-4-carbonitrile **31** on standing in the presence of daylight turns blue in colour. TLC indicated the formation of an unidentified highly polar (baseline) blue coloured product together with starting isothiazole **31**. This light sensitivity was confirmed when a fresh solution kept in the dark gave no colour change. The identification of this product is outside of the scope of the present study.

Furthermore, while the methoxyphenyl, chlorophenyl and thienyl substituents were unaffected by the hydrazine treatment, the reaction of 3-chloro-5-(3-nitrophenyl)isothiazole-4-carbonitrile **27** with anhydrous hydrazine gave a second product, 5-(3-anilino)-3-chloropyrazole-4-carbonitrile **52**. Hydrazine in the presence of a transition metal catalyst is well known to reduce nitro to amino groups.[60,61] A pure recrystallised sample of 3-amino-5-(3-nitrophenyl)pyrazole-4-carbonitrile **27** treated with hydrazine and KOH in MeOH at ca. 20 °C for 4 d in the absence of any transition metal catalyst gave the (3-anilino)pyrazole **52** in 97% yield. Interestingly the reduction of the nitro group could be avoided with the use of hydrazine monohydrate in DMSO at ca. 20 °C for 40 min which converted the isothiazole **27** into the desired 3-nitrophenylpyrazole-4-carbonitrile **46** in 90% yield (Scheme 3).

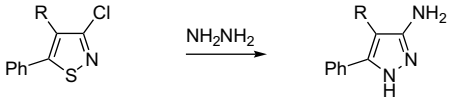


Scheme 3. Reagents and conditions: (i) **27** (0.19 mmol), $NH_2NH_2 \cdot H_2O$ (0.5 mL), 20 °C, DMSO (1.5 mL), 40 min, 90%; (ii) **46** (0.19 mmol), NH_2NH_2 (2 equiv), KOH (3 equiv), MeOH, 4 d, 20 °C, 97%.

2.3. Varying the isothiazole C-4 substituent with a nucleofuge at C-3

The isothiazole C-4 nitrile could be involved in the isothiazole into pyrazole transformation. As such several isothiazoles with a variety of C-4 substituents (**55** R=H, **56** R=Br, **57** R=Ph and **58** R=NH_2) were subjected to anhydrous hydrazine to elucidate the influence of the C-4 substituents (Table 4).

Table 4
Reaction of 3-chloro-5-phenyl-4-substituted isothiazoles **1**, **55–58** (0.230 mmol) in anhydrous hydrazine (2 mL)

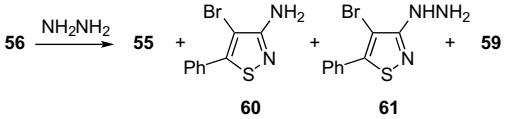


	R	Temp (°C)	Time (h)	Yields (%)
1	CN	20	0.25	**2** (99)
55	H	20	7	**59** (70)
55	H	200[a]	0.5	**59** (72)
56	Br	20	27	Complex[b]
57	Ph	20	24	Complex[c]
58	NH_2	20	24	V. complex
58	NH_2	200[a]	48	V. complex

[a] Sealed tube.
[b] Refer to Table 5.
[c] Refer to Table 8.

3-Chloro-5-phenylisothiazole **55** was converted cleanly into the corresponding 3-amino-5-phenylpyrazole **59** (70%), but required a long reaction time (7 h) compared to the 4-carbonitrile derivative **1**. Introducing the reaction mixture (sealed tube) into a preheated Wood's metal bath at 200 °C gave a substantially shorter reaction time (0.5 h) and comparable yield (72%). This supported that the C-4 nitrile was not essential for the ring transformation to occur but tentatively assisted the reaction by enhancing the electrophilicity of the isothiazole C-5 position. The 4-bromo- and 4-phenylisothiazoles **56** and **57** gave complex reaction mixtures which were studied

Table 5
Reaction of 4-bromo-3-chloro-5-phenylisothiazole **56** (0.230 mmol) with anhdrous hydrazine (2 mL)



Temp (°C)	Time (h)	Yields (%)			
		55	**60**	**61**	**59**
20	27	11	29	18	26
20–110	2.5	34	25	14	20
110	0.5	20	55	16	7
150[a]	5 min	0	5	82	6
200[a]	3 min	0	0	86	4

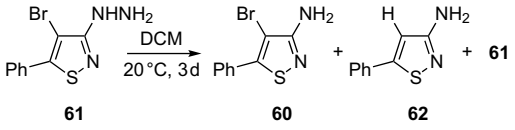
[a] Sealed tube.

further (Tables 5–8), while 4-amino-3-chloro-5-phenylisothiazole **58** gave a reaction mixture that was too complex to analyse.

At ca. 20 °C 4-bromo-3-chloro-5-phenylisothiazole **56** required 27 h to be consumed by anhydrous hydrazine and the reaction gave four products but not 3-amino-4-bromo-5-phenylpyrazole. The first and fourth products isolated by chromatography were 3-chloro-5-phenylisothiazole **55** in which chemoselective protodehalogenation had occurred at C-4 and the corresponding 3-amino-5-phenylpyrazole **59**. Unlike the reduction of the nitro group (Scheme 3) the use of hydrazine monohydrate in DMSO failed to prevent the protodehalogenation at C-4. Hydrazine is known to reduce alkyl and aryl halides.[60] Suprisingly the second and third products were 3-amino-4-bromo-5-phenylisothiazole **60** and 4-bromo-3-hydrazino-5-phenylisothiazole **61**. Since arylhydrazines are known to suffer autoreductive conversion to give anilines[62] it was possible that the 3-aminoisothiazole **60** was derived from the 3-hydrazinylisothiazole **61**. While 3-hydrazinyl benzoisothiazole was reported,[63] to the best of our knowledge monocyclic 3-hydrazinylisothiazoles are not known and only a few unsubstituted 5-hydrazinyl monocyclic isothiazoles have been reported,[49,51–55,64] together with only two reports of trisubstituted 4-hydrazinylisothiazoles.[65,66] To our delight performing the reaction at high temperature in a preheated (200 °C) Wood's metal bath for a short duration (3 min) followed by a rapid quench in crushed ice gave 4-bromo-3-hydrazino-5-phenylisothiazole **61** in high yield (86%). This allowed for a careful study of the novel 4-bromo-3-hydrazino-5-phenylisothiazole **61**.

A 2D silica TLC stability study showed that the 3-hydrazinylisothiazole **61** was unstable and converted into the 3-aminoisothiazole **60**. Furthermore a degassed DCM solution of 3-hydrazinylisothiazole **61** under an argon or air atmosphere after 3 d led to a 64–62% conversion of 3-hydrazinylisothiazole **61** into 3-amino-4-bromo-5-phenylisothiazole **60** (56–49%) and 3-aminoisothiazole **62** (43–51%). After 3 d under a pure O_2 atmosphere a similar quantity of the 3-hydrazinylisothiazole **61** was consumed (60%), however, a significantly improved yield of 3-amino-4-bromo-5-phenylisothiazole **60** (89%) together with a significantly reduced amount of the protodebrominated 3-aminoisothiazole **62** (11%) were obtained (Table 6).

Table 6
Stability of the 3-hydrazinylisothiazole **61** (0.074 mmol) in DCM (1 mL) under various atmospheres at ca. 20 °C for 3 d



61 **60** **62**

Atmosphere	Yields[a] (%)		
	60	**62**	**61**
Ar	56	43	36
Air	49	51	38
O_2	89	11	40

[a] Yields based on recovered 3-hydrazinylisothiazole **61**.

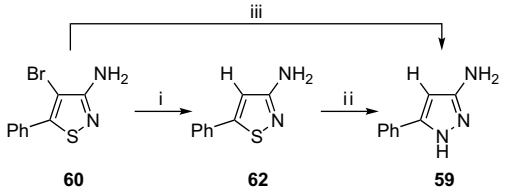
Interestingly treating 4-bromo-3-hydrazino-5-phenylisothiazole **61** with neat anhydrous hydrazine under an air atmosphere at ca. 20 °C for only 35 min gave a clean conversion to 3-amino-4-bromo-5-phenylisothiazole **60** (96%). Although when the reaction was repeated in neat degassed anhydrous hydrazine under an argon atmosphere the conversion (**61**→**60**) was incomplete after 1 d. Suprisingly under a pure oxygen atmosphere the reaction was still slow but after 25 h the conversion (**61**→**60**) was complete and high yielding (98%). Furthermore on prolonged reaction times (2 d) at ca. 20 °C or under reflux (110 °C) the reaction mixture became more complex and both the protodebrominated 3-amino-5-phenylisothiazole **62** and the 3-amino-5-phenylpyrazole **59** could be isolated. Prolonged heating (6 d) at 110 °C gave 3-amino-5-phenylpyrazole **59** as the major product (81%) (Table 7).

Table 7
Reaction of the 3-hydrazinylisothiazole **61** (0.100 mmol) with anhydrous hydrazine (1 mL) under an atmosphere of air

Temp (°C)	Time (d)	Yields[a] (%)		
		60	**62**	**59**
20	35 min	96	0	0
20	1[a]	91[b]	0	0
20	2	26	45	20
20	25 h[c]	98	0	0
110	1	0	39	55
110	6	0	9	81

[a] Degassed hydrazine under an argon atmosphere.
[b] Based on (30%) recovered 3-hydrazinylisothiazole **61**.
[c] Under an oxygen atmosphere.

Attempts to directly obtain a high yield of 3-amino-5-phenylisothiazole **62** from 4-bromo-3-hydrazino-5-phenylisothiazole **61** were not successful (Table 7). Nevertheless, treating 3-amino-4-bromo-5-phenylisothiazole **60** with anhydrous hydrazine at ca. 20 °C for 35 h gave only the protodebrominated 3-amino-5-phenylisothiazole **62** in high yield (90%). Heating either 3-amino-4-bromo- or 3-amino-5-phenylisothiazole **60** & **62** with anhydrous hydrazine at 110 °C for 4 and 5 d gave 3-amino-5-phenylpyrazole **59** in 80% (8% recovered starting isothiazole **62**) and 81% yields respectively (Scheme 4).



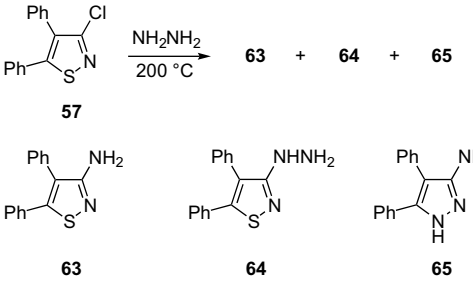
60 **62** **59**

Scheme 4. Reagents and conditions: (i) N_2H_4, 20 °C, 35 h, 90%; (ii) N_2H_4, 110 °C, 4 d, 80%; (iii) N_2H_4, 110 °C, 5 d, 81%.

The reaction of 3-chloro-4,5-diphenylisothiazole **57** with anhydrous hydrazine at 20 °C gave a complex reaction mixture (Table 4), but the product distribution was simplified when the reaction was performed in a sealed tube at 200 °C (Wood's metal bath) for 20 min, giving mainly 3-hydrazino-4,5-diphenylisothiazole **64** in good yield (77%) together with some unreacted starting isothiazole **57**. Prolonged heating (35 min) gave two new products, 3-amino-4,5-diphenylisothiazole **63** and 3-amino-4,5-diphenylpyrazole **65** (Table 8). Extending the heating period to 2 h led to an increase in the formation of 3-aminoisothiazole **63** and the 3-amino-4,5-diphenylpyrazole **65** at the expense of 3-hydrazino-4,5-diphenylisothiazole **64**.

The stability of the 3-hydrazino-4,5-diphenylisothiazole **64** was investigated further. Rather suprisingly DCM solutions of 3-hydrazino-4,5-diphenylisothiazole **64** under air, argon and oxygen atmospheres for 3 d at ca. 20 °C, gave no reaction products and the 3-hydrazino-4,5-diphenylisothiazole **64** was quantitatively recovered unchanged. This stability was in stark contrast with that of the 4-bromo-3-hydrazino-5-phenylisothiazole **61** (Table 7). While this difference in stability remains to be explained the formation of the 3-hydrazinylisothiazoles **61** and **64** under thermodynamically driven conditions (200 °C) provides a rather precarious yet novel route to these previously unreported 3-hydrazine functionalized isothiazoles. The analogous attempts to prepare 3-hydrazino-5-

Table 8
Reaction of 3-chloro-4,5-diphenylisothiazole **57** (0.185 mmol) with anhydrous hydrazine (2 mL) in a sealed tube at 200 °C



Time (min)	Yields (%)		
	63	**64**	**65**
20	0	77 (87)[a]	0
35	39	40	21
2 h	60	0	33

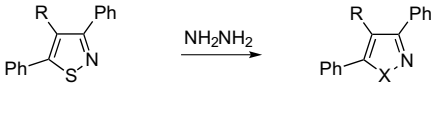
[a] Yield based on recovered 3-chloro-4,5-diphenylisothiazole **57**.

phenylisothiazole-4-carbonitrile **3** from 3-chloro-5-phenylisothiazole-4-carbonitrile **1** only afforded pyrazole **2**.

2.4. Varying the isothiazole C-4 substituent without a nucleofuge at C-3

When the substituent at the isothiazole C-3 position was not a leaving group the conversion into pyrazole proceeded only under relatively very harsh conditions; no reactions were observed at room temperature (Table 9).

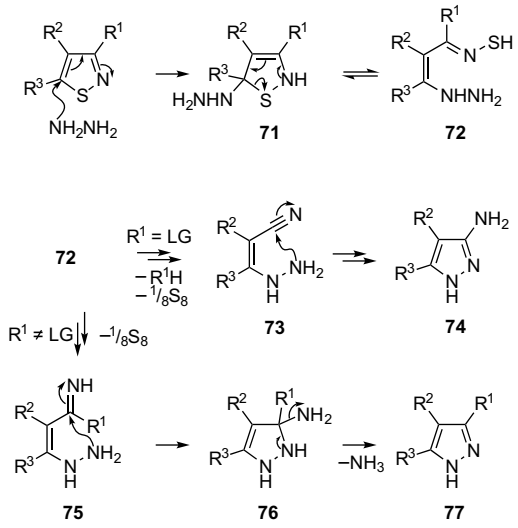
Table 9
Reaction of 3,5-diphenyl-4-substituted isothiazoles **11**, **66**–**69** (0.230 mmol) in anhydrous hydrazine (2 mL) in a sealed reaction tube



	R	Temp (°C)	Time (d)	Yields (%)
11	CN	150	1	**16** (X=NH, R=CN) (83)
66	H	200	7	nr[a]
67	Br	200	2.5 h	**66** (X=S, R=H) (100)
68	Ph	200	3	nr[a]
69	NH_2	150	20	**70** (X=NH, R=NH_2) (20)[b]

[a] nr=no reaction.
[b] Based on 49% recovered 4-amino-3,5-diphenylisothiazole **69**.

4-Bromo-3,5-diphenylisothiazole **67** suffered only quantitative protodebromination to afford 3,5-diphenylisothiazole **66** which showed no further reaction with anhydrous hydrazine. Prolonged heating in a sealed tube or the use of a CEM Discover microwave reactor at 200 °C for 20 min failed to convert or consume either 3,5-diphenyl- or 3,4,5-triphenyl-isothiazoles **66** and **69** respectively. These examples identified one of the limits for the isothiazole into pyrazole conversion using neat anhydrous hydrazine. The high yield conversion of the 4-cyano isothiazole **11** was presumably owed to the powerful electron withdrawing effect of the nitrile which provided some activation for the isothiazole into pyrazole conversion, although at the reaction temperature (150 °C) and based on the isolation of 3-hydrazinylisothiazoles **61** and **64** the initial site of attack by hydrazine could in this case be the isothiazole C-3 position (see Scheme 5 below).



Scheme 5.

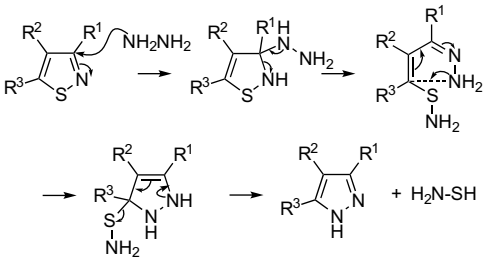
2.5. Mechanistic rationale

In light of the above, rational mechanisms could be proposed to explain the formation of the pyrazoles depending on the leaving ability of the isothiazole C-3 substituent (Scheme 4). Initially hydrazine could attack the highly electrophilic isothiazole C-5 carbon[48–50] to afford the 2,5-dihydroisothiazole **71** that could be in equilibrium with its ring opened form **72**. When R^1 was a good leaving group (e.g., R^1=Cl), loss of R^1H and sulfur could give the hydrazinyl acrylonitrile **73**. Intramolecular cyclisation and subsequent tautomerisation would afford the 3-aminopyrazole **74**. The intramolecular cyclisation of β-hydrazinyl acrylonitriles into 3-aminopyrazoles has been reported to be rapid and independent of *E*/*Z* alkene geometry.[67,68] Where R^1 was not or was a poor leaving group the ring opened intermediate **72** could lose sulfur to afford the hydrazinyl enimine **75**, which could suffer intramolecular cyclisation to give the 1,3-dihydropyrazole **76** and ultimately the fully aromatic pyrazole **77**.

The reaction mixtures showed no elemental sulfur as would be expected since anhydrous hydrazine was known to reduce sulfur rapidly to hydrogen sulfide which then can form $(N_2H_4)_2{\cdot}H_2S$ and $N_2H_4{\cdot}H_2S$ salts with the excess hydrazine.[69] Indeed the reaction mixtures gave a strong odour of hydrogen sulfide [WARNING TOXIC] and its presence was confirmed using Accuro pump fitted with a hydrogen sulfide Dräger tube which tested positive. It was not clear whether hydrogen sulfide was formed directly from the reaction or from elemental sulfur which could have originated from the reaction mixture. However, nucleophilic attack on isothiazole in the absence of a good nucleofuge at C-5 is normally expected to occur on the ring sulfur.[70,71] Since this possibility can not be eliminated based on the observed experimental data, initial nucleophilic attack at sulfur could also be the initiation point for this ring transformation, although the failure to convert 3-chloro-5-(2,6-dimethylphenyl)isothiazole-4-carbonitrile **28** into the corresponding pyrazole suggested that when the isothiazole C-5 position was sterically hindered then attack at C-3 was preferential to attack at the ring sulfur.

Furthermore in light of the initial formation and isolation of 3-hydrazinylisothiazoles **61** and **64** during the high temperature reactions with anhydrous hydrazine an alternative mechanism must be considered for the high temperature (150 °C) ring transformation of 3,5-diphenylisothiazole-4-carbonitrile **11** into 3,5-diphenylpyrazole-4-carbonitrile **16**. In this case, hydrazine

could initially attack the isothiazole C-3 carbon and a ring opening–ring closure sequence ultimately releasing the observed pyrazole and possibly a species equivalent to thiohydroxylamine[72] (Scheme 6).

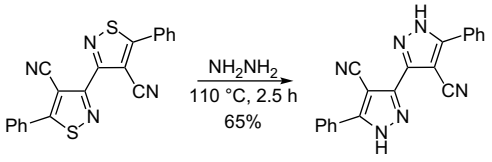


Scheme 6.

Regardless of which pathways are proposed this ring transformation clearly belongs to the Assisted Nucleophilic Ring Opening Ring Closing ANRORC family.[73,74]

2.6. Conversion of biisothiazoles into bipyrazoles

The conversion of isothiazoles into pyrazoles using neat anhydrous hydrazine could be extended without complication to the known 5,5′-diphenyl-3,3′-biisothiazole-4,4′-dicarbonitrile **78** which was readily transformed into 5,5′-diphenyl-3,3′-bi(1*H*-pyrazole)-4,4′-dicarbonitrile **79** in 65% yield. Similar treatment of 5,5′-bi(3-chloroisothiazole-4-carbonitrile) with hydrazine, however, gave only a complex reaction mixture from which no products could be isolated and characterised.

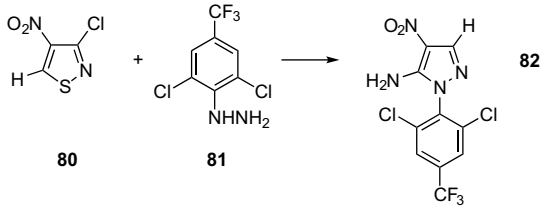


78 **79**

Many bipyrazoles are known, and several 3,3′- and 5,5′-bipyrazoles have shown interesting biological activities.[75–77]

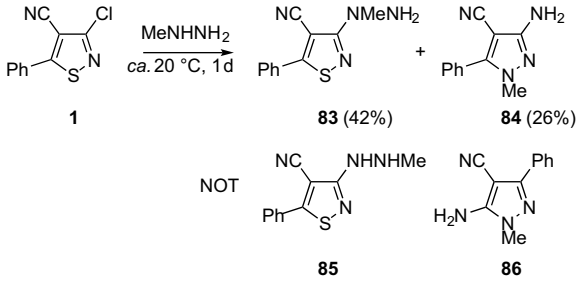
2.7. Methylhydrazine

The conversion of isothiazoles into pyrazoles has been shown to proceed with hydrazine, both in its hydrated and anhydrous form. Only one example currently exists where the conversion has been achieved with a substituted hydrazine. 3-Chloro-4-nitroisothiazole **80** was converted into 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-nitropyrazole **82** using 2,6-dichloro-4-trifluoromethylphenylhydrazine **81**.[46] Assuming the initial attack occurred at the isothiazole C-5 position then the arylhydrazine appeared to have attacked via its β-nitrogen. A logical extension of our current study was therefore to investigate the action of methylhydrazine on isothiazoles.



80 **81** **82**

3-Chloro-5-phenylisothiazole-4-carbonitrile **1** treated with methylhydrazine at ca. 20 °C for 1 d gave two products, 3-(1-methylhydrazino)-5-phenylisothiazole-4-carbonitrile **83** in 42% and 3-amino-1-methyl-5-phenylpyrazole-4-carbonitrile **84** in 27% yield.



1 **83** (42%) **84** (26%)

NOT

85 **86**

The structural elucidation of the reaction products was complicated owing to the possibility of alternative isomeric structures isothiazole **85** and pyrazole **86**. Nevertheless, the two possible isothiazole isomers **83** and **85** could be tentatively differentiated by their ^{1}H NMR spectra. The 1,2-disubstituted unsymmetrical hydrazine **85** was expected to show two separate NH resonances which should integrate in a ratio of 1:1, while the 1,1-disubstituted hydrazine **83** should show only one NH_2 resonance the integration of which should show two protons. The ^{1}H NMR of the isolated isothiazole gave a single broad peak at 4.02 ppm the integration of which showed two protons and supported the structure to be isothiazole **83**. Fortunately the two possible pyrazole isomers had both been previously prepared independently with no ambiguity in their reported structures. These two pyrazoles had significantly different melting points, 3-amino-1-methyl-5-phenylpyrazole-4-carbonitrile **84** (mp 158 °C)[78] and 5-amino-1-methyl-3-phenylpyrazole-4-carbonitrile **86** (mp 134 °C from H_2O).[79] The isolated pyrazole (mp 158 °C from EtOH) matched the melting point of the reported pyrazole **84**. Both products clearly indicated a preference for the methylhydrazine to attack through the α-nitrogen bearing the methyl substituent which was unlike the preference of the arylhydrazine that preferred to attack through the β-nitrogen.

3. Summary

The use of hydrazine to convert isothiazoles into pyrazoles has been investigated with respect to substitution patterns on the isothiazole at C-3, C-4 and C-5. The data tentatively suggests that in the absence of steric hindrance the hydrazine attacks initially the isothiazole C-5 carbon and that this is followed by ring opening and subsequent ring closure to give pyrazoles. When the isothiazole C-5 substituent is not a good nucleofuge and the C-3 substituent is a good nucleofuge the use of high temperatures and short reaction times can lead to the formation of 3-hydrazinylisothiazoles. When both the C-3 and C-5 substituents are not leaving groups the isothiazoles can be transformed into pyrazoles only under harsh conditions and the presence of a nitrile at C-4 assists this transformation. The isothiazole into pyrazole conversion can be extended to methylhydrazine which preferentially attacks through its α-nitrogen.

4. Experimental

4.1. General

Anhydrous hydrazine was prepared by distillation of hydrazine monohydrate from KOH under argon and stored over 4 Å molecular sieves. DMF was azeotropically distilled with PhH then distilled under

vacuum from anhydrous $MgSO_4$ and stored over 4 Å molecular sieves. Reactions were protected by $CaCl_2$ drying tubes or performed under an argon atmosphere. Anhydrous Na_2SO_4 was used for drying organic extracts and all volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used throughout for all non-TLC scale chromatographic separations using Merck Silica Gel 60 (less than 0.063 mm). A CEM Discover Microwave Reactor was used for microwave experiments. Chemglass heavy wall cylindrical pressure vessels (15 mL) with a Teflon bushing as a pressure seal were used for the sealed tube studies. Melting points were determined using a PolyTherm-A, Wagner & Munz, Koefler—Hotstage Microscope apparatus. Solvents used for recrystallization are indicated after the melting point. UV spectra were obtained using a Perkin-Elmer Lambda-25 UV/vis spectrophotometer and inflections are identified by the abbreviation 'inf'. IR spectra were recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer with Pike *Miracle* Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 machine (at 300 and 75 MHz respectively). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GCMS with direct inlet probe. Microanalysis were performed at London Metropolitan University. 3-Chloro-5-phenylisothiazole-4-carbonitrile **1**, 3-bromo-5-phenylisothiazole-4-carbonitrile **4**,[50] 3-methoxy-5-phenylisothiazole-4-carbonitrile **6**,[80] 3-iodo-5-phenylisothiazole-4-carbonitrile **5**, 3-hydroxy-5-phenylisothiazole-4-carbonitrile **7**, 3-amino-5-phenylisothiazole-4-carbonitrile **8** and 3-benzylamino-5-phenylisothiazole-4-carbonitrile **9** and 3,5-diphenylisothiazole-4-carbonitrile **11**,[12] 3-*N*-morpholino-5-phenylisothiazole-4-carbonitrile **10**,[81] 3-chloro-5-(*m*-tolyl)isothiazole-4-carbonitrile **19**, 3-chloro-5-(2-methoxyphenyl)isothiazole-4-carbonitrile **20**, 3-chloro-5-(3-methoxyphenyl)isothiazole-4-carbonitrile **21**, 3-chloro-5-(4-methoxyphenyl)-isothiazole-4-carbonitrile **22**, 3-chloro-5-(3-thienyl)isothiazole-4-carbonitrile **23**, 3-chloro-5-(2-chlorophenyl)isothiazole-4-carbonitrile **24**, 3-chloro-5-(3-chlorophenyl)isothiazole-4-carbonitrile **25**, 3-chloro-5-(4-chlorophenyl)isothiazole-4-carbonitrile **26** and 3-chloro-5-(3-nitrophenyl)isothiazole-4-carbonitrile **27**,[12] 5-amino-3-chloroisothiazole-4-carbonitrile **30**, 3-chloro-5-hydrazinylisothiazole-4-carbonitrile **31**, 3-chloro-5-(*N*-phenylamino)isothiazole-4-carbonitrile **32**, 3-chloro-5-methoxyisothiazole-4-carbonitrile **34**, 3-chloro-5-phenoxyisothiazole-4-carbonitrile **35**, 3-chloro-5-(phenylthio)isothiazole-4-carbonitrile **36** and 3,5-dichloroisothiazole-4-carbonitrile **37**,[49] 3-chloro-5-phenylisothiazole **55**, 4-bromo-3-chloro-5-phenylisothiazole **56**, 3-chloro-4,5-diphenylisothiazole **57**, 4-amino-3-chloro-5-phenylisothiazole **58**, 3,5-diphenylisothiazole **66**, 4-bromo-3,5-diphenylisothiazole **67**, 3,4,5-triphenylisothiazole **68**, 4-amino-3,5-diphenylisothiazole **69** and 3-amino-4,5-diphenylisothiazole **63**[82] were prepared according to literature procedures.

4.2. 3-Amino-5-phenylpyrazole-4-carbonitrile 2 (see Table 1)

To a stirred mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **1** (50 mg, 0.23 mmol) in DMSO (1 mL), protected with $CaCl_2$ drying tube at ca. 20 °C, hydrazine monohydrate (1.9 mL, 0.046 mol) was added. The reaction mixture was held at this temperature until no starting material remained (by TLC) and was then poured onto crushed ice (50 g) and extracted with Et_2O (2×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/Et_2O, 3:7 and then Et_2O 100%) gave the title compound **2** (39 mg, 92%) as a white powder, mp 194–195 °C (lit.,[13] 200 °C) (from EtOH/H_2O); R_f (Et_2O) 0.55; identical to an authentic sample.

4.3. 3-Amino-5-phenylpyrazole-4-carbonitrile 2 (Table 2)

A mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **1** (50 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), protected with $CaCl_2$ drying tube was stirred at ca. 20 °C until no starting material remained (TLC). The reaction mixture was then poured onto crushed ice (50 g). The precipitate which formed was collected by filtration to afford the title compound **2** (42 mg, 99%) as a white powder, mp 194–195 °C (lit.,[13] 200 °C) (from EtOH/H_2O) identical to that described above.

4.4. 3-Amino-5-phenylpyrazole-4-carbonitrile 2 (from 3-bromoisothiazole 4)

Similar treatment of 3-bromo-5-phenylisothiazole-4-carbonitrile **4** (61 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) gave the title compound **2** (42 mg, 100%) as a white powder, mp 194–195 °C (lit.,[13] 200 °C) (from EtOH/H_2O) identical to that described above.

4.5. 3-Amino-5-phenylpyrazole-4-carbonitrile 2 (from 3-iodoisothiazole 5)

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **5** (72 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) gave the title compound **2** (41 mg, 98%) as a white powder, mp 194–195 °C (lit.,[13] 200 °C) (from EtOH/H_2O) identical to that described above.

4.6. 3-Methoxy-5-phenyl-1*H*-pyrazole-4-carbonitrile 12

A mixture of 3-methoxy-5-phenylisothiazole-4-carbonitrile **6** (46 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), protected with a $CaCl_2$ drying tube, was stirred at ca. 20 °C until no starting material remained (TLC). The reaction mixture was then poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 1:1) gave the *title compound* **12** (25 mg, 52%) as colourless needles, mp 181–182 °C (from EtOH); R_f (hexane/EtOAc, 1:1) 0.65; [Found: C, 66.4; H, 4.6; N, 21.0. $C_{11}H_9N_3O$ requires C, 66.3; H, 4.6; N, 21.1%]; λ_{max} (EtOAc)/nm 262 (log ε 2.97); ν_{max}/cm^{-1} 3183w (NH_2), 3119w, 3017w, 2961w (Ar CH), 2853w (Ph CH), 2818w (Ph CH), 2232m (C≡N), 1589w, 1568w, 1537s, 1512s, 1493m, 1458w, 1444w, 1418s, 1331w, 1258w, 1196w, 1158w, 1142m, 1131m, 1040w, 1011m, 961w, 920w, 777m, 751w, 725s, 713m; δ_H (300 MHz; DMSO-d_6) 13.33 (1H, br s, N*H*), 7.81–7.70 (2H, m, Ph C*H*), 7.62–7.46 (3H, m, Ph C*H*), 3.95 (3H, s, CH_3); δ_C (75 MHz; DMSO-d_6) 164.5, 147.15, 130.4 (Ph *C*H), 129.3 (Ph *C*H), 126.7, 126.2 (Ph *C*H), 114.0 (*C*≡N), 74.1 (*C*C≡N), 56.45 (*C*H_3); δ_C (75 MHz; DEPT-135, DMSO-d_6) 130.4 (Ph *C*H), 129.3 (Ph *C*H), 126.2 (Ph *C*H), 56.4 (*C*H_3); *m*/*z* (EI) 199 (M^+, 100%), 198 (M^+-1, 53), 170 (38), 156 (7), 142 (12), 127 (50), 115 (11), 104 (75), 100 (29), 77 ($C_6H_5^+$, 83), 63 (15), 51 (58). Further elution (EtOAc, 100%) gave 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **2** (20 mg, 48%) as a white powder, mp 194–195 °C (lit.,[13] 200 °C) (from EtOH/H_2O); R_f (EtOAc) 0.75; identical to an authentic sample.

4.7. 3-Hydroxy-5-phenyl-1*H*-pyrazole-4-carbonitrile 13

Similar treatment of 3-hydroxy-5-phenylisothiazole-4-carbonitrile **7** (47 mg, 0.23 mmol) with anhydrous hydrazine gave after chromatography (hexane/Et_2O, 7:3 and then Et_2O 100%) the *title compound* **13** (41 mg, 97%) as colourless needles, mp 141.5–143.5 °C (from pentane/EtOH); R_f (Et_2O) 0.30; [Found: C, 64.8; H, 3.9; N, 22.6. $C_{10}H_7N_3O$ requires C, 64.9; H, 3.8; N, 22.7%]; λ_{max} (MeOH)/nm 237 (log ε 4.42), 260 inf (4.41), 296 inf (4.26), 312 inf (4.12), 326 inf (3.87); ν_{max}/cm^{-1} 3333w & br (OH), 2957w (Ph CH), 2924m (Ph CH), 2853w (Ph CH), 2203w (C≡N), 1643m, 1589m, 1514w, 1485m, 1449w, 1433w, 1377w, 1275w, 1123w, 1098w, 1072w, 1030w, 970w, 918w, 860w,

797w, 766w, 743w, 725s; δ_H (300 MHz; DMSO-d_6) (1 peak missing) 13.28 (1H, br s, N*H* or O*H*), 7.76–7.61 (5H, m, Ph C*H*); δ_C (300 MHz; DMSO-d_6) 173.8, 168.6, 131.7 (Ph *C*H), 129.7 (Ph *C*H), 128.1, 126.9 (Ph *C*H), 113.4 (*C*≡N), 93.0 (*CC*≡N); *m*/*z* (EI) 185 (M^+, 24), 128 (42), 121 (11), 104 (30), 91 (50), 86 (67), 77 ($C_6H_5^+$, 100), 57 (38), 51 (41).

4.8. 3-(*N*-Benzylamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile 14

Similar treatment of 3-benzylamino-5-phenylisothiazole-4-carbonitrile **9** (67 mg, 0.23 mmol) with anhydrous hydrazine gave after chromatography (hexane/Et_2O, 7:3) the *title compound* **14** (34 mg, 54%) as pale yellow plates, mp 206–208 °C (from EtOH); R_f (hexane/Et_2O, 7:3) 0.13; [Found: C, 74.4; H, 5.1; N, 20.4. $C_{17}H_{14}N_4$ requires C, 74.4; H, 5.1; N, 20.4%]; λ_{max} (MeOH)/nm 209 (log ε 3.20), 237 (3.11); ν_{max}/cm^{-1} 3360m (NH), 3184w, 3150w, 3105w, 3086w (Ph CH), 3055w (Ph CH), 3028w (Ph CH), 2951w, 2918w, 2884w, 2837w, 2803w, 2218s (C≡N), 1587m, 1570s, 1524m, 1495m, 1466w, 1452m, 1429w, 1350m, 1327w, 1306w, 1234w, 1196w, 1161w, 1130w, 1080m, 1058w, 1030w, 986w, 959w, 916w, 837w, 797w, 770m, 731s; δ_H (300 MHz; DMSO-d_6) 12.62 (1H, br s, N*H*), 7.78 (2H, d, *J* 7.2, Ph *H*), 7.51–7.30 (8H, m, Ph *H* and N*H*), 7.25–7.21 (1H, m, Ph *H*), 4.40 (2H, d, *J* 6, CH_2); δ_C [75 MHz; DMSO-d_6 with Cr(acac)$_3$] (1 peak missing) 156.2 (w & br), 150.95 (w & br), 139.45, 129.5 (Ph *C*H), 129.0 (Ph *C*H), 128.3 (Ph *C*H), 127.3 (Ph *C*H), 126.9 (Ph *C*H), 125.9 (Ph *C*H), 116.0 (*C*≡N), 70.0 [w & br, (*CC*≡N)], 46.2 (*C*H$_2$); δ_C (75 MHz; DEPT-135, DMSO-d_6) 129.5 (Ph *C*H), 129.0 (Ph *C*H), 128.3 (Ph *C*H), 127.3 (Ph *C*H), 126.9 (Ph *C*H), 125.9 (Ph *C*H); *m*/*z* (EI) 274 (M^+, 24%), 197 ($M^+-C_6H_5$, 8), 170 (4), 127 (6), 104 (4), 91 ($C_6H_5CH_2^+$, 100), 77 ($C_6H_5^+$, 12), 51 (7). Further elution (Et_2O, 100%) gave 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **2** (14 mg, 33%) as a white powder, mp 194–195 °C (lit.,[13] 200 °C) (from EtOH/H_2O), R_f (Et_2O) 0.55; identical to an authentic sample.

4.9. 3-Morpholino-5-phenyl-1*H*-pyrazole-4-carbonitrile 15

A mixture of 3-morpholino-5-phenylisothiazole-4-carbonitrile **10** (62 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was heated to ca. 80 °C until no starting material remained (TLC). The reaction mixture was allowed to cool to ca. 20 °C, poured onto crushed ice (50 g) and extracted with Et_2O (3×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/Et_2O, 3:7) gave the *title compound* **15** (35 mg, 59%) as colourless needles, mp 184.5–185 °C (from EtOH); R_f (hexane/Et_2O, 3:7) 0.50; [Found: C, 66.2; H, 5.5; N, 21.9. $C_{14}H_{14}N_4O$ requires C, 66.1; H, 5.55; N, 22.0%]; λ_{max} (MeOH)/nm 207 (log ε 3.15), 211 (3.11), 235 (3.04), 254 inf (2.98); ν_{max}/cm^{-1} 3214w & br (NH), 2960w (Ph CH), 2917w (Ph CH), 2860w and 2832w (CH$_2$), 2218s (C≡N), 1565m, 1512s, 1495s, 1456m, 1436w, 1377m, 1305m, 1287m, 1281m, 1264w, 1239w, 1151m, 1121s, 1072w, 1052w, 1045w, 1030w, 968s, 917s, 858w, 844m, 777s; δ_H (300 MHz; CD_2Cl_2) 7.75–7.71 (2H, m, Ph *H*), 7.53–7.50 (3H, m, Ph *H*), 3.82 (4H, dd, *J* 4.8, CH_2N), 3.42 (4H, dd, *J* 5.6, 4.1, CH_2O); δ_C (75 MHz; DMSO-d_6) (1 peak missing) 160.1 (w & br), 148.1 (w & br), 129.9 (Ph *C*), 129.1 (Ph *C*H), 128.3, 126.4 (Ph *C*H), 116.4 (*C*≡N), 76.4 [w & br (*CC*≡N)], 65.5 (*C*H$_2$O), 48.0 (*C*H$_2$N); δ_C (75 MHz; DEPT-135, DMSO-d_6) (1 peak missing) 129.1 (Ph *C*H), 126.4 (Ph *C*H), 65.5 (*C*H$_2$O), 48.0 (*C*H$_2$N); *m*/*z* (EI) 254 (M^+, 91%), 239 (35), 223 (17), 196 (67), 169 (23), 140 (10), 127 (15), 104 (100), 77 ($C_6H_5^+$, 48), 57 (29). Further elution (Et_2O, 100%) gave 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **2** (16 mg, 38%) as a white powder, mp 194–195 °C (lit.,[13] 200 °C) (from EtOH/H_2O), R_f (Et_2O) 0.55; identical to an authentic sample.

4.10. 3,5-Diphenyl-1*H*-pyrazole-4-carbonitrile 16

A mixture of 3,5-diphenylisothiazole-4-carbonitrile **11** (45 mg, 0.23 mmol) and anhydrous hydrazine in a sealed tube, was introduced into a preheated Wood's metal bath at 150 °C and was stirred until no starting material remained (TLC). The reaction mixture was then allowed to cool to ca. 20 °C, poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried and evaporated to afford the title compound **16** (26 mg, 83%) as colourless needles, mp 220.5–221.5 °C (lit.,[83] 230 °C) (from EtOH); λ_{max} (*t*-BuOMe)/nm 208 (log ε 3.42), 248 (3.45); ν_{max}/cm^{-1} 3181 br & w (NH), 3024w (Ph CH), 2228m (C≡N), 1564w, 1486m, 1450w, 1444m, 1431w, 1402w, 1319w, 1297w, 1279w, 1254w, 1137m, 1074m, 1027w, 1002w, 964s, 918w, 777s, 733m, 717s; δ_H (300 MHz; $CDCl_3$) 10.82 (1H, br s, N*H*), 7.92–7.89 (4H, m, Ph *H*), 7.55–7.48 (6H, m, Ph *H*); δ_C (75 MHz; DMSO-d_6) 153.1, 148.6, 130.9, 129.3, 126.6, 115.8 (*C*≡N), 109.4, 85.4 (*CC*≡N); *m*/*z* (EI) 245 (M^+, 100%), 216 (10), 189 (6), 142 (4), 122 (5), 115 (6), 104 (7), 94 (7), 77 ($C_6H_5^+$, 21), 63 (5), 51 (13).

4.11. 1-Benzyl-3-(dibenzylamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile 18 (see Scheme 2)

To a stirred mixture of 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **2** (50 mg, 0.27 mmol) and potassium hydroxide (182 mg, 3.24 mmol) in DMF (2 mL) at ca. 20 °C, benzyl bromide (32 μL, 0.27 mmol) was added. The reaction mixture was held at this temperature until no starting material remained (TLC). The mixture was diluted with EtOAc and extracted with H_2O (3×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (EtOAc/hexane, 3:7) gave 3-(*N*-benzylamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile **14** (24 mg, 33%), mp 206–208 °C (from EtOH), identical to that described above. Further elution (EtOAc, 100%) gave the *title compound* **18** as colourless needles (23 mg, 57%), mp 118.5–120.5 °C (from EtOH); R_f (EtOAc) 0.93; [Found C, 81.9; H, 5.7; N, 12.2. $C_{31}H_{26}N_4$ requires C, 81.9; H, 5.8; N, 12.3%]; λ_{max} (EtOAc)/nm 253 (log ε 3.52); ν_{max}/cm^{-1} 3077w (Ph CH), 3042w (Ph CH), 2854w, 2217m (C≡N), 1607w, 1586w, 1527m, 1495w, 1474m, 1453m, 1451m, 1436w, 1400w, 1367m, 1359m, 1324w, 1288w, 1266w, 1228w, 1211w, 1180w, 1154w, 1140w, 1098w, 1074w, 1041w, 1030w, 1016w, 1003w, 968w, 936w, 919w, 904w, 846w, 833w, 779s, 758s, 749s, 731m, 719m; δ_H (300 MHz; $CDCl_3$) 7.99–7.97 (2H, d, *J* 6, Ph *H*), 7.49–7.18 (16H, m, Ph *H*), 7.10–7.03 (2H, m, Ph *H*), 5.11 (2H, s, NCH_2Ph), 4.28 [4H, s, N(CH_2Ph)$_2$]; δ_C (75 MHz; $CDCl_3$) (1 peak missing) 154.9, 151.6, 136.1, 135.7, 131.1, 129.1 (Ph *C*H), 128.9 (Ph *C*H), 128.7 (Ph *C*H), 128.6 (Ph *C*H), 127.9 (Ph *C*H), 127.8 (Ph *C*H), 127.0 (Ph *C*H), 126.3 (Ph *C*H), 115.1 (*C*≡N), 84.1 (*CC*≡N), 57.3 (*C*H$_2$), 51.45 (*C*H$_2$); δ_C (75 MHz; DEPT-135, $CDCl_3$) (1 peak missing) 129.1 (Ph *C*H), 128.9 (Ph *C*H), 128.7 (Ph *C*H), 128.6 (Ph *C*H), 127.9 (Ph *C*H), 127.8 (Ph *C*H), 127.0 (Ph *C*H), 126.3 (Ph *C*H), 57.3 [N(*C*H$_2$Ph)$_2$], 51.45 (NCH_2Ph); *m*/*z* (EI) 454 (M^+, 9%), 363 (M^+-PhCH_2, 7), 199 (40), 170 (9), 143 (7), 116 (8), 91 ($PhCH_2^+$, 100), 77 ($C_6H_5^+$, 6), 74 (14), 65 (19).

4.12. 3-(Benzylideneamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile 17 (see Scheme 2)

A mixture of 3-amino-5-phenylpyrazole-4-carbonitrile **2** (50 mg, 0.27 mmol) and PhCHO (1 mL, 9.72 mmol) was stirred at ca. 20 °C until no starting material remained (TLC). The reaction mixture was diluted with Et_2O and extracted with saturated solution of sodium bisulfate (4×50 mL) to remove unreacted benzaldehyde. The organic extracts were combined, dried and evaporated to give the *title compound* **17** (53 mg, 72%) as yellow plates, mp 174–175 °C (from EtOH); [Found C, 74.9; H, 4.4; N, 20.5. $C_{17}H_{12}N_4$ requires C, 75.0; H, 4.4; N, 20.6%]; λ_{max} (*t*-BuOMe)/nm 205 (log ε 4.35), 228 (4.22), 263 (4.18); ν_{max}/cm^{-1} 3202w & br (NH), 3119w (Ph CH), 3059w (Ph CH), 3030w (Ph CH), 2232m (C≡N), 1620s, 1599w, 1574m, 1493m, 1458m, 1429w, 1348w, 1314w, 1296w, 1275w, 1213m, 1159w, 1111m, 1078w, 1001w, 984w, 972m, 922w, 876w,

849w, 800w, 777w, 760s; δ_H (300 MHz; DMSO-d_6) 14.05 (s, 1H, N*H*), 9.08 (s, 1H, N=C*H*), 8.01 (d, 2H, *J* 6.9, Ph *H*), 7.88 (d, 2*H*, *J* 6.9, Ph *H*), 7.68–7.50 (m, 6H, *J* 7.2, Ph *H*); δ_C (75 MHz; DMSO-d_6) 163.7 (N=CH), 147.7, 134.9, 134.5, 132.7, 130.1, 129.4, 129.2, 129.0, 126.2, 125.6, 114.7 (*C*≡N), 83.2 (*CC*≡N); *m*/*z* (EI) 272 (M^+, 11%), 271 (M^+-1, 11), 184 (15), 172 (51), 155 (5), 128 (11), 115 (12), 104 (11), 91 ($PhCH_2^+$, 100), 77 ($C_6H_5^+$, 20), 65 (14).

4.13. 3-(*N*-Benzylamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile 14 (See Scheme 2)

To a stirred mixture of 3-(benzylideneamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile **17** (30 mg, 0.11 mmol) in MeOH (2 mL) under argon at ca. 0 °C, $NaBH_4$ (68.2 mg, 0.22 mmol) was added in one portion. The reaction left to warm to ca. 20 °C until no starting material remained (TLC). The reaction mixture was diluted with EtOAc and extracted with H_2O (3×50 mL). The organic extracts were combined, dried and evaporated to afford the *title compound* **14** (30 mg, 100%) as pale yellow plates, mp 206–208 °C (from EtOH), identical to that described above.

4.14. 3-Amino-5-phenyl-1*H*-pyrazole-4-carbonitrile 2 (see Scheme 2)

In a suspension of 3-(*N*-benzylamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile **14** (30 mg, 0.11 mmol) in H_2O at ca. 20 °C, MeOH (176 μL, 5%) was added. The reaction mixture held at this temperature until no starting material remained (TLC) and was then diluted with H_2O and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried and evaporated to afford the title compound **2** (20 mg, 99%), as a white powder, mp 194–195 °C (lit.,[13] 200 °C) (from EtOH/H_2O) identical to an authentic sample.

4.15. 3-Amino-5-*m*-tolyl-1*H*-pyrazole-4-carbonitrile 38

A mixture of 3-chloro-5-*m*-tolylisothiazole-4-carbonitrile **19** (54 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), protected with a $CaCl_2$ drying tube, was stirred at ca. 20 °C until no starting material remained (TLC). The reaction mixture was poured onto crushed ice (50 g) and exracted with EtOAc (4×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 3:7) gave the *title compound* **38** (44 mg, 97%) as colourless needles, mp 194.5–195.5 °C (from EtOH); R_f (hexane/EtOAc, 3:7) 0.65; [Found: C, 66.6; H, 5.0; N, 28.2. $C_{11}H_{10}N_4$ requires C, 66.6; H, 5.1; N, 28.3%]; λ_{max} (MeOH)/nm 209 (log ε 2.76), 231 (2.52), 255 (2.45); ν_{max}/cm^{-1} 3365w and 3299w (NH_2), 3279w, 3206 m and 3184m (NH), 3139w, 3101w, 3060w, 3050w and 3012w (Ph CH), 2959w and 2912w (CH_3), 2226s (C≡N), 1646m, 1575m, 1534s, 1506m, 1483m, 1398w, 1344w, 1168w, 1082m, 1017w, 984w, 898w, 882w, 854m, 786s, 747s, 727s; δ_H (300 MHz; DMSO-d_6) 12.18 (1H, s, N*H*), 7.63–7.55 (2H, m, Ph C*H*), 7.39–7.29 (1H, br m, Ph C*H*), 7.24–7.16 (1H, br m, Ph C*H*), 6.44 (2H, br s, NH_2), 2.34 (3H, s, CH_3); δ_C (75 MHz; DMSO-d_6) 154.7 (w & br), 150.0 (w & br), 137.9 (Ph *C*H), 131.9 (w & br), 129.3 (w & br), 128.7 (Ph *C*H), 126.2 (Ph *C*H), 122.8 (Ph *C*H), 116.2 (*C*≡N), 69.6 (*CC*≡N), 21.1 (CH_3); δ_C (75 MHz; DEPT-135, DMSO-d_6) 129.3 (Ph *C*H), 128.7 (Ph *C*H), 126.2 (Ph *C*H), 122.8 (Ph *C*H), 21.1 (CH_3); *m*/*z* (EI) 199 (M^++1, 16), 198 (M^+, 100%), 197 (M^+-1, 16), 180 (9), 170 (4), 155 (8), 142 (4), 115 (3), 91 (2), 77 ($C_6H_5^+$, 1).

4.16. 3-Amino-5-(2-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile 39

Similar treatment of 3-amino-5-(2-methoxyphenyl)isothiazole-4-carbonitrile **20** (58 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the title compound **39** (47 mg, 95%) as pale yellow plates, mp 179–180 °C (lit.,[84] 192 °C) (from EtOH); R_f (hexane/EtOAc, 3:7) 0.65; [Found: C, 61.7; H, 4.8; N, 26.1. $C_{11}H_{10}N_4O$ requires C, 61.7; H, 4.7; N, 26.1%]; λ_{max} (MeOH)/nm 213 (log ε 3.13), 259 (2.83), 287 inf (2.73); ν_{max}/cm^{-1} 3413w (NH_2), 3326w and 3295w (NH), 3186w (Ph CH), 2211m (C≡N), 1636m, 1602w, 1587m, 1558m, 1524m, 1484m, 1457m, 1449w, 1432w, 1307w, 1269m, 1251m, 1187w, 1167w, 1120w, 1071m, 1023m, 969m, 945w, 807w, 768s, 752m, 706m; δ_H (300 MHz; DMSO-d_6) tautomeric mixture of isomers 12.43 (1H, br s, N*H*), 12.11 (1H, br s, N*H*), 7.50–7.35 (4H, m, Ph C*H*), 7.20–7.10 (2H, m, Ph C*H*), 7.10–6.95 (2H, m, Ph C*H*), 6.27 (2H, br s, NH_2), 5.50 (2H, br s, NH_2), 3.80 (6H, s, CH_3); δ_C (75 MHz; DMSO-d_6) 156.6, 153.8 (w & br), 149.4 (w & br), 130.7 (w & br), 129.6 (w & br), 120.6 (Ph *C*H), 115.8 (*C*≡N), 111.8 (Ph *C*H), 73.5 (w & br) (*CC*≡N), 55.4 (OCH_3); δ_C (75 MHz; DEPT-135, DMSO-d_6) 120.6 (Ph *C*H), 111.8 (Ph *C*H), 55.4 (OCH_3); *m*/*z* (EI) 214 (M^+, 100%), 198 (5), 185 (11), 171 (9), 155 (4), 144 (11), 129 (6), 116 (11), 101 (5), 89 (11), 77 ($C_6H_5^+$, 5), 63 (4).

4.17. 3-Amino-5-(3-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile 40

Similar treatment of 3-amino-5-(3-methoxyphenyl)isothiazole-4-carbonitrile **21** (58 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the *title compound* **40** (44 mg, 90%) as colourless needles, mp 132–133 °C (from EtOH); R_f (hexane/EtOAc, 3:7) 0.65; [Found: C, 61.6; H, 4.7; N, 26.0. $C_{11}H_{10}N_4O$ requires C, 61.7; H, 4.7; N, 26.1%]; λ_{max} (MeOH)/nm 219 (log ε 3.21), 255 (2.89), 290 inf (2.66); ν_{max}/cm^{-1} 3428w (NH_2), 3349w, 3218w (NH), 3165w (Ph CH), 2962w, 2936w, 2914w and 2833w (CH_3), 2211s (C≡N), 1637s, 1614m, 1604m, 1597m, 1583m, 1520s, 1462m, 1430m, 1350m, 1316w, 1287m, 1275w, 1230s, 1183w, 1144w, 1106w, 1091w, 1049s, 1000m, 991m, 892m, 880w, 849m, 789m, 783m, 762w, 733m; δ_H (300 MHz; DMSO-d_6) 12.21 (1H, s, N*H*), 7.38–7.34 (3H, m, Ph C*H*), 6.97 (1H, br s, Ph C*H*), 6.49 (2H, br s, NH_2), 3.78 (3H, s, OCH_3); δ_C (75 MHz; DMSO-d_6) 159.3, 154.6, 149.8, 133.4, 129.8 (Ph *C*H), 117.9 (Ph *C*H), 116.3 (*C*≡N), 114.1 (Ph *C*H), 110.9 (Ph *C*H), 69.5 (*CC*≡N), 55.0 (OCH_3); δ_C (75 MHz; DEPT-135, DMSO-d_6) 129.8 (Ph *C*H), 117.9 (Ph *C*H), 114.1 (Ph *C*H), 110.9 (Ph *C*H), 55.0 (OCH_3); *m*/*z* (EI) 214 (M^+, 100%), 199 (3), 185 (22), 171 (12), 158 (6), 142 (14), 129 (6), 116 (12), 107 (8), 102 (4), 89 (11), 88 (7), 77 ($C_6H_5^+$, 7), 63 (7), 51 (4).

4.18. 3-Amino-5-(4-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile 41

Similar treatment of 3-amino-5-(4-methoxyphenyl)isothiazole-4-carbonitrile **22** (58 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the title compound **41** (42 mg, 94%) as colourless needles, mp 170.5–171.5 °C (lit.,[85] 183–186 °C) (from EtOH); R_f (hexane/EtOAc, 3:7) 0.65; [Found: C, 61.6; H, 4.6; N, 26.1. $C_{11}H_{10}N_4O$ requires C, 61.7; H, 4.7; N, 26.1%]; λ_{max} (MeOH)/nm 207 (log ε 3.01), 262 (2.84); ν_{max}/cm^{-1} 3464w, 3427w (NH_2), 3362w, 3321w (NH), 3179w (Ph CH), 2219w and 2206m (C≡N), 1653w, 1627m, 1613m, 1587w, 1532s, 1509w, 1502w, 1489m, 1482m, 1434m, 1292m, 1261s, 1253s, 1189m, 1159w, 1138w, 1065w, 1024m, 1011w, 968w, 829s, 803w, 780w, 737m, 714w; δ_H (300 MHz; DMSO-d_6) 12.08 (1H, s, N*H*), 7.74–7.72 (2H, d, *J* 8.4, Ph C*H*), 7.05–7.02 (2H, d, *J* 8.1, Ph C*H*), 6.41 (2H, s, NH_2), 3.79 (3H, s, OCH_3); δ_C (75 MHz; DMSO-d_6) 159.6, 154.7, 149.8, 127.1 (Ph *C*H), 124.7, 116.4 (*C*≡N), 114.2 (Ph *C*H), 69.3 (*CC*≡N), 55.2 (OCH_3); δ_C (75 MHz; DEPT-135, DMSO-d_6) 127.1 (Ph *C*H), 114.2 (Ph *C*H), 55.2 (OCH_3); *m*/*z* (EI) 214 (M^+, 100%), 199 (30), 185 (3), 171 (17), 157 (3), 143 (6), 129 (3), 116 (8), 114 (5), 107 (4), 89 (7), 77 ($C_6H_5^+$, 3), 63 (4).

4.19. 3-Amino-5-(thien-3-yl)-1*H*-pyrazole-4-carbonitrile 42

Similar treatment of 3-amino-5-(thien-3-yl)isothiazole-4-carbonitrile **23** (52 mg, 0.23 mmol) with anhydrous hydrazine (2 mL)

gave the *title compound* **42** (41 mg, 94%) as colourless needles, mp 224.5–225.5 °C (from EtOH); R_f (hexane/EtOAc, 3:7) 0.65; [Found: C, 50.5; H, 3.2; N, 29.4. $C_8H_6N_4S$ requires C, 50.5; H, 3.2; N, 29.4%]; λ_{max} (MeOH)/nm 210 (log ε 3.05), 263 (2.93); ν_{max}/cm^{-1} 3419w and 3341w (NH_2), 3226w (NH), 3163w, 3111w, 3028w, 2966w (Ph CH), 2898w (Ph CH), 2838w (Ph CH), 2213s (C≡N), 1634s, 1596m, 1559w, 1521s, 1456m, 1379m, 1339m, 1272w, 1081w, 1003s, 891m, 860m, 814w, 784s, 723s; δ_H (300 MHz; $CDCl_3$/drop of DMSO-d_6) (1 peak missing), 7.75 (1H, s, thienyl C*H*), 7.45 (1H, d, *J* 4.8, thienyl C*H*), 7.24–7.22 (1H, m, thienyl C*H*), 4.86 (2H, s, NH_2); δ_C (75 MHz; DMSO-d_6) 154.1, 146.7, 133.5, 126.9 (thienyl *C*H), 125.5 (thienyl *C*H), 121.9 (thienyl *C*H), 116.3 (*C*≡N), 69.4 (*CC*≡N); δ_C (75 MHz; DEPT-135, DMSO-d_6) 126.9 (thienyl *C*H), 125.5 (thienyl *C*H), 121.9 (thienyl *C*H); *m*/*z* (EI) 190 (M$^+$, 100%), 161 (14), 148 (9), 134 (12), 121 (3), 108 (3), 95 (4), 90 (4), 76 (3), 63 (4).

4.20. 3-Amino-5-(2-chlorophenyl)-1*H*-pyrazole-4-carbonitrile 43[86]

Similar treatment of 3-amino-5-(2-chlorophenyl)isothiazole-4-carbonitrile **24** (59 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the title compound **43** (42 mg, 87%) as colourless needles, mp 184–189 °C (from EtOH); R_f (hexane/EtOAc, 3:7) 0.65; [Found: C, 55.0; H, 3.1; N, 25.7. $C_{10}H_7N_4Cl$ requires C, 54.9; H, 3.2; N, 25.6%]; λ_{max} (MeOH)/nm 212 (log ε 3.15), 228 inf (2.94), 267 inf (2.44); ν_{max}/cm^{-1} 3198m (NH_2), 3183m (NH), 3173w and 3166w and 3159w (Ph CH), 2225m (C≡N), 1647w, 1636w, 1624w, 1582w, 1565m, 1555w, 1532m, 1528m, 1500m, 1490w, 1473w, 1465w, 1457w, 1437w, 1395w, 1324w, 1282w, 1259w, 1254w, 1168w, 1104w, 1081m, 1058m, 1045w, 986m, 972w, 879w, 851w, 830w, 788m, 777w, 769w, 755s, 729s, 720s; δ_H (300 MHz; DMSO-d_6) 12.215 (1H, s, N*H*), 7.58–7.45 (4H, m, Ph C*H*), 6.45 (2H, s, NH_2); δ_C (75 MHz; DMSO-d_6) 153.5, 149.8, 132.1, 131.45 (Ph *C*H), 130.5 (Ph *C*H), 129.7 (Ph *C*H), 129.15, 127.1 (Ph *C*H), 115.1 (*C*≡N), 72.9; δ_C (75 MHz; DEPT-135, DMSO-d_6) 131.45 (Ph *C*H), 130.5 (Ph *C*H), 129.7 (Ph *C*H), 127.1 (Ph *C*H); m/z (EI) 218 (M$^+$, 100%), 220 (32), 189 (6), 183 (M$^+$−Cl, 5), 176 (11), 155 (17), 126 (27), 114 (8), 100 (23), 87 (8), 77 ($C_6H_5^+$, 22), 63 (15), 51 (25).

4.21. 3-Amino-5-(3-chlorophenyl)-1*H*-pyrazole-4-carbonitrile 44

Similar treatment of 3-amino-5-(3-chlorophenyl)isothiazole-4-carbonitrile **25** (59 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the *title compound* **44** (45 mg, 90%) as colourless needles, mp 211–212 °C (from EtOH); R_f (hexane/EtOAc, 3:7) 0.65; [Found: C, 55.0; H, 3.3; N, 25.6. $C_{10}H_7N_4Cl$ requires C, 54.9; H, 3.2; N, 25.6%]; λ_{max} (MeOH)/nm 256 (log ε 3.18), 275 inf (3.06); ν_{max}/cm^{-1} 3362w (NH_2), 3303w (NH), 3295w, 3199m, 3169m, 3140w, 3127w and 3095w (Ph CH), 3069w (Ph CH), 3048w (Ph CH), 2227s (C≡N), 1642m, 1582m, 1565m, 1532s, 1500m, 1474m, 1437w, 1423w, 1406w, 1396w, 1343w, 1314w, 1168w, 1104w, 1082m, 987m, 907w, 879m, 811w, 787s, 777m, 744m, 728s; δ_H (300 MHz; DMSO-d_6) 12.37 (1H, s, N*H*), 7.79–7.74 (2H, m, Ph C*H*), 7.53–7.44 (2H, m, Ph C*H*), 6.5 (2H, s, NH_2); δ_C (75 MHz; DMSO-d_6) 155.2, 147.9, 133.5, 131.5, 130.8 (Ph *C*H), 128.5 (Ph *C*H), 125.1 (Ph *C*H), 124.1 (Ph *C*H), 116.0 (*C*≡N), 70.1 (*CC*≡N); δ_C (75 MHz; DEPT-135, DMSO-d_6) 130.8 (Ph *C*H), 128.5 (Ph *C*H), 125.1 (Ph *C*H), 124.1 (Ph *C*H); *m*/*z* (EI) 218 (M$^+$, 100%), 220 (33), 189 (12), 176 (7), 162 (20), 153 (6), 1127 (26), 114 (13), 99 (24), 85 (18), 77 ($C_6H_5^+$, 23), 63 (18), 57 (53).

4.22. 3-Amino-5-(4-chlorophenyl)-1*H*-pyrazole-4-carbonitrile 45

Similar treatment of 3-amino-5-(4-chlorophenyl)isothiazole-4-carbonitrile **26** (59 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the title compound **45** (46 mg, 92%) as colourless needles, mp 209–212 °C (lit.,[87] 212 °C) (from EtOH); [Found: C, 55.0; H, 3.2; N, 25.5. $C_{10}H_7N_4Cl$ requires: C, 54.9; H, 3.2; N, 25.6%]; λ_{max} (MeOH)/nm 209 (log ε 3.11), 238 inf (3.07), 257 (3.13); ν_{max}/cm^{-1} 3344w (NH_2), 3296w, 3201m (NH), 3138w and 3122w and 3071w and 3045w (Ph CH), 2958w, 2917w, 2849w, 2223s (C≡N), 1647w, 1605w, 1582w, 1531s, 1489s, 1424w, 1420w, 1383w, 1347w, 1341w, 1173w, 1139w, 1097m, 1086m, 1016w, 967w, 825s, 817m, 769m, 733s; δ_H (300 MHz; DMSO-d_6) 12.24 (1H, s, N*H*), 7.82–7.79 (2H, m, Ph C*H*), 7.55–7.52 (2H, m, Ph C*H*), 6.54 (2H, s, NH_2); δ_C (75 MHz; DMSO-d_6) 154.7, 148.8, 133.1 (Ph *C*H), 130.9 (Ph *C*H), 128.8 (Ph *C*H), 127.2 (Ph *C*H), 116.1 (*C*≡N), 69.4 (*CC*≡N); δ_C (75 MHz; DEPT-135, DMSO-d_6) 128.8 (Ph *C*H), 127.2 (Ph *C*H); *m*/*z* (EI) 220 (M$^+$+2, 13%), 218 (M$^+$, 39), 189 (4), 176 (4), 153 (4), 126 (12), 111 (16), 99 (14), 85 (29), 77 ($C_6H_5^+$, 11), 71 (47), 63 (6), 57 (91).

4.23. 3-Amino-5-(3-nitrophenyl)-1*H*-pyrazole-4-carbonitrile 46[85] and 3-amino-5-(3-aminophenyl)-1*H*-pyrazole-4-carbonitrile 52

Similar treatment of 3-amino-5-(3-nitrophenyl)isothiazole-4-carbonitrile **27** (61 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave two products. Chromatography (hexane/Et_2O, 3:2) gave the title compound **46** (38 mg, 72%) as yellow plates, mp 251–252 °C (from EtOH); R_f (hexane/Et_2O, 3:2) 0.40; [Found C, 52.5, H, 3.0, N, 30.6. $C_{10}H_7N_5O_2$ requires C, 52.4; H, 3.1; N, 30.6%]; λ_{max} (MeOH)/nm 234 (log ε 3.08), 254 (3.10); ν_{max}/cm^{-1} 3460w (NH_2), 3428w, 3396w, 3360w, 3207w (Ph CH), 2924w (Ph CH), 2854w (Ph CH), 2213m (C≡N), 1652m, 1627m, 1616m, 1597w, 1576w, 1532m, 1516m, 1511m, 1498m, 1351s, 1110w, 1072w, 998w, 900w, 893w, 879w, 822w, 798w, 792w, 748w, 736w, 715s; δ_H (300 MHz; DMSO-d_6) 12.42 (1H, s, N*H*), 8.61 (1H, dd, *J* 1.7, 1.65, Ph C*H*), 8.23 (2H, m, Ph C*H*), 7.76 (1H, t, *J* 8.1, Ph C*H*), 6.65 (2H, s, NH_2); δ_C (75 MHz; DMSO-d_6) 154.9, 148.1, 147.7, 133.5, 131.5 (Ph *C*H), 130.5 (Ph *C*H), 123.1 (Ph *C*H), 119.7 (Ph *C*H), 115.8 (*C*≡N), 69.6 (*CC*≡N); δ_C (75 MHz; DEPT-135, DMSO-d_6) 131.5 (Ph *C*H), 130.5 (Ph *C*H), 123.1 (Ph *C*H), 119.7 (Ph *C*H); *m*/*z* (EI) 229 (M$^+$, 100%), 183 (18), 156 (13), 141 (4), 129 (21), 114 (14), 101 (7), 99 (4), 77 ($C_6H_5^+$, 7), 63 (4). Further elution (Et_2O, 100%) gave *3-amino-5-(3-aminophenyl)-1*H*-pyrazole-4-carbonitrile* **52** as colourless needles (13 mg, 28%), mp >300 °C (from EtOH); R_f (Et_2O) 0.20; [Found: C, 60.4; H, 4.5; N, 35.2. $C_{10}H_9N_5$ requires C, 60.3; H, 4.55; N, 35.2%]; λ_{max} (MeOH)/nm 207 (log ε 2.55), 265 (3.17); ν_{max}/cm^{-1} 3447m, 3330m (NH_2), 3250m, 3210m (NH), 2918w (Ph CH), 2851w (Ph CH), 2209s (C≡N), 1647s, 1636s, 1596s, 1517s, 1463m, 1448m, 1437m, 1333w, 1307w, 1265w, 1242w, 1074m, 1014w, 1008w, 926w, 900w, 878w, 797m, 727s; δ_H (300 MHz; DMSO-d_6) 12.18 (1H, s, N*H*), 7.08 (1H, t, *J* 7.6, Ph C*H*), 6.97 (1H, s, Ph C*H*), 6.91 (1H, d, *J* 7.5, Ph C*H*), 6.59 (1H, d, *J* 7.5, Ph C*H*), 6.11 (2H, s, NH_2), 5.22 (2H, s, C_6H_4 NH_2); δ_C (75 MHz; DMSO-d_6) 148.8, 131.7, 129.1, 128.7, 128.6, 116.1 (*C*≡N), 114.5, 113.4, 111.0, 71.0 (*CC*≡N); *m*/*z* (EI) 199 (M$^+$, 100%), 170 (19), 155 (10), 143 (14), 116 (9), 99 (6), 89 (7), 77 ($C_6H_5^+$, 4), 63 (6), 57 (5).

4.24. 3-Chloro-5-(2,6-dimethylphenyl)isothiazole-4-carbonitrile 28

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **37** (100 mg, 0.56 mmol), 2,6-dimethylphenylboronic acid (226 mg, 1.51 mmol), KF (179 mg, 3.07 mmol), $Pd(OAc)_2$ (6 mg, 5 mol %) and 18-crown-6 (74 mg, 0.28 mmol, 0.5 equiv) in dry and degassed DMF (2 mL) under an argon atmosphere, was heated to ca. 110 °C, until no starting material remained (TLC). The mixture was allowed to cool to ca. 20 °C, diluted with DCM and washed with H_2O (4×50 mL). The organic layer was separated, dried and adsorbed on silica. Chromatography (hexane/DCM, 1:1) gave the *title compound* **28** (42 mg, 30%) as colourless needles, mp 73–74 °C (from

cyclohexane); R_f (hexane/DCM, 1:1) 0.50; [Found: C, 58.2; H, 3.5; N, 11.3. $C_{12}H_9ClN_2S$ requires C, 58.0; H, 3.6; N, 11.3%]; λ_{max} (DCM)/nm 228 (log ε 2.71), 268 (2.59), 298 (2.46); ν_{max}/cm^{-1} 2235w, 1514w, 1507w, 1463w, 1448w, 1420w, 1388w, 1381w, 1344m, 1309w, 1226w, 1169w, 1104w, 1043w, 833m, 811w, 779s, 737w, 723w, 705w; δ_H (300 MHz; $CDCl_3$) 7.35–7.30 (1H, m, Ph C*H*), 7.2–7.18 (2H, m, Ph C*H*), 2.18 (6H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 176.9, 150.5, 136.1, 130.9 (Ph *C*H), 128.2 (Ph *C*H), 125.7, 110.8 (*C*≡N), 109.4, 20.2 (*C*H$_3$); δ_C (75 MHz; DEPT-135, $CDCl_3$) 130.9 (Ph *C*H), 128.2 (Ph *C*H), 20.2 (*C*H$_3$); *m*/*z* (EI) 250 (M$^+$+2, 27%), 248 (M$^+$, 71), 233 (4), 213 (M$^+$−Cl, 100), 206 (6), 186 (36), 169 (10), 159 (9), 153 (12), 147 (7), 140 (17), 127 (16), 115 (20), 103 (12), 93 (27), 77 ($C_6H_5^+$, 50), 63 (31), 51 (35).

4.25. 3-Amino-5-(2,6-dimethylphenyl)-1*H*-isothiazole-4-carbonitrile 53

A mixture of 3-chloro-5-(2,6-dimethylphenyl)isothiazole-4-carbonitrile **28** (61 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), protected with a $CaCl_2$ drying tube, was stirred at ca. 20 °C until no starting material remained (TLC). The reaction mixture was poured onto crushed ice (50 g) and extracted with EtOAc (4×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 7:3) gave the *title compound* **53** (39 mg, 70%) as pale yellow crystals, mp 145 °C (from EtOH/H_2O); R_f (hexane/EtOAc, 7:3) 0.63; [Found C, 62.9; H, 4.8; N, 18.4. $C_{12}H_{11}N_3S$ requires C, 62.9; H, 4.8; N, 18.3%]; λ_{max} (*t*-BuOMe)/nm 206 (log ε 3.99), 305 (3.92); ν_{max}/cm^{-1} 3408m and 3320w (NH_2), 3215w (NH), 2920w (CH_3), 2230m (C≡N), 1641m, 1551s, 1486m, 1464w, 1429w, 1396w, 1382w, 1313w, 1261w, 1227w, 1165w, 1117w, 1096w, 1037w, 964w, 892w, 843m, 776s, 743m, 725m; δ_H (300 MHz; DMSO-d_6) 7.35–7.30 (1H, m, Ph C*H*-4), 7.24–7.21 (2H, m, Ph C*H*-3 & 5), 6.96 (2H, br s, NH_2), 2.13 (6H, s, CH_3); δ_C (75 MHz; DMSO-d_6) 173.7, 164.9, 136.15, 129.95 (Ph *C*H-4), 127.8 (Ph *C*H-3 & 5), 127.3, 112.7 (*C*≡N), 96.5 (*C*C≡N), 19.6 (*C*H$_3$); δ_C (75 MHz; DEPT-135, DMSO-d_6) 129.95 (Ph *C*H-4), 127.8 (Ph *C*H-3 & 5), 19.6 (*C*H$_3$); *m*/*z* (EI) 229 (M$^+$, 100%), 214 (8), 211 (10), 197 (6), 186 (18), 172 (8), 160 (9), 140 (8), 127 (9), 115 (10), 77 ($C_6H_5^+$, 8), 63 (5).

4.26. 3-Chloro-5-(*N*-morpholino)isothiazole-4-carbonitrile 29

In a stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **37** (0.5 g, 2.8 mmol) in EtOH (50 mL) at ca. 20 °C, protected with a $CaCl_2$ drying tube, morpholine (0.49 g, 5.60 mmol) was added and the reaction mixture stirred at this temperature until no starting material remained (TLC). The precipitate which formed was collected by filtration to afford the *title compound* **29** (577 mg, 90%) as colourless needles, mp 129–129.5 °C (from cyclohexane); λ_{max} (DCM)/nm 229 (log ε 2.0), 280 (1.9); ν_{max}/cm^{-1} 2978w, 2914w, 2870w, 2210m (C≡N), 1558s, 1537s, 1506w, 1483s, 1466w, 1441m, 1387w, 1354w, 1341w, 1308m, 1294s, 1275m, 1250w, 1117s, 1065w, 1057w, 982m, 951s, 903w, 800m, 789m; δ_H (300 MHz; $CDCl_3$) 3.87–3.84 (4H, t, *J* 5.1, CH_2O), 3.60–3.57 (4H, t, *J* 4.9, CH_2N); δ_C (75 MHz; $CDCl_3$) 179.4, 150.3, 113.9, 85.8, 65.5 (*C*H$_2$O), 49.5 (*C*H$_2$N); *m*/*z* (EI) 231 (M$^+$+2, 38%), 229 (M$^+$, 100), 214 (10), 194 (6), 171 (85), 164 (12), 144 (25), 109 (84), 82 (16), 57 (34).

4.27. 3-Amino-5-(*N*-morpholino)-1*H*-pyrazole-4-carbonitrile 47

A mixture of 3-chloro-5-(*N*-morpholino)isothiazole-4-carbonitrile **29** (53 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), protected with a $CaCl_2$ drying tube, was stirred at ca. 20 °C until no starting material remained (TLC). The reaction mixture was poured onto crushed ice (50 g) and extracted with EtOAc (4×50 mL). The organic extracts were combined and evaporated to give the title compound **47** as colourless needles, mp 98.5–99.5 °C (from EtOH); [Found C, 49.7; H, 5.8; N, 36.3. $C_8H_{11}N_5O$ requires C, 49.7; H, 5.7; N, 36.3%]; λ_{max} (*t*-BuOMe)/nm 210 (log ε 3.08), 232 inf (2.72), 259 inf (2.10); ν_{max}/cm^{-1} 3381m, 3337w, 3275w, 3219w, 3177m, 3024w, 2951w, 2876w and 2832w (CH_2), 2207s (C≡N), 1668s, 1624s, 1607s, 1541s, 1520m, 1493s, 1445m, 1369m, 1335w, 1317w, 1310w, 1288w, 1269w, 1254m, 1186w, 1138w, 1115s, 1074w, 1047w, 1026m, 999w, 912s, 853w, 777w, 731m; δ_H (300 MHz; DMSO-d_6); 11.07 (1H, s, N*H*), 6.12 (2H, s, NH_2), 3.66 (4H, br s, CH_2N), 3.12 (4H, br s, CH_2O); δ_C (75 MHz; DMSO-d_6) 168.6, 154.2, 116.35 (*C*≡N), 65.5 (*C*H$_2$O), 62.0 (*C*C≡N), 47.9 (*C*H$_2$N); *m*/*z* (EI) 193 (M$^+$, 73%), 178 (26), 162 (11), 149 (5), 135 (100), 122 (3), 108 (28), 92 (8), 80 (16), 79 (18), 66 (27), 57 (9).

4.28. 3,5-Diamino-1*H*-pyrazole-4-carbonitrile 48

A mixture of 5-amino-3-chloroisothiazole-4-carbonitrile **30** (37 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at ca. 20 °C for 5 min until no starting material remained (TLC). The reaction mixture was poured onto crushed ice (50 g) and the aqueous mixture was then evaporated. The residue obtained was passed through a short pad (2 cm) of silica that was then washed well with *t*-BuOMe. Removal of the volatiles gave the title compound **48** (24 mg, 84%) as colourless needles, mp 170–171 °C, (lit.,[88] 169–170 °C) (from EtOH); λ_{max} (*t*-BuOMe)/nm 276 (log ε 3.41); ν_{max}/cm^{-1} 3236w, 3212w and 3050w (NH), 1683m, 1666s, 1648m, 1631w, 1544s, 1437w, 1367m, 1289m, 1253s, 1117m, 1049m, 984w; δ_H (300 MHz; DMSO-d_6) 8.94 (1H, s, N*H*), 4.13 (2H, s, NH_2); δ_C (75 MHz; DMSO-d_6) 175.2, 169.5, 168.9 (1 peak missing); *m*/*z* (EI) 123 (M$^+$, 12%), 97 (M$^+$−CN, 11), 83 (11), 74 (9), 69 (14), 57 (30), 55 (21).

4.29. 3-Amino-1*H*-pyrazole-4-carbonitrile 54

A mixture of 3-chloro-5-hydrazinoisothiazole-4-carbonitrile **31** (40 mg, 0.23 mmol) in anhydrous hydrazine (2 mL), was stirred at ca. 110 °C until no starting material remained (TLC). The reaction mixture was allowed to cool to ca. 20 °C, poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 1:1) gave 3,5-diamino-1*H*-pyrazole-4-carbonitrile **48** (25 mg, 86%) as colourless needles, mp 170–171 °C, (lit.,[88] 169–170 °C) (from EtOH), identical to that described above. Further elution (EtOAc, 100%), gave 3-amino-1*H*-pyrazole-4-carbonitrile **54** (3 mg, 13%) as a colourless powder, mp 173–174 °C (lit.,[89] 172 °C); R_f (EtOAc) 0.93; δ_H (300 MHz; DMSO-d_6) 12.05 (1H, s, N*H*), 7.64 (2H, br & w, NH_2), 6.30 (1H, s, C*H*), identical to an authentic sample.

4.30. 3-Amino-5-(*N*-phenylamino)-1*H*-pyrazole-4-carbonitrile 49

A mixture of 3-chloro-5-(*N*-phenylamino)isothiazole-4-carbonitrile **32** (54 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), was stirred at ca. 110 °C until no starting material remained (TLC). The reaction mixture was allowed to cool to ca. 20 °C and was poured onto crushed ice (50 g). The aqueous mixture was then evaporated and the residue obtained was passed through a short pad (2 cm) of silica that was then washed well with *t*-BuOMe. Removal of the volatiles gave the title compound **49** (41 mg, 91%) as pink plates, mp 195–196 °C (lit.,[90] 205 °C) (EtOH/cyclohexane); λ_{max} (*t*-BuOMe)/nm 206 (log ε 3.54), 222 inf (3.43), 263 (3.49), 367 (1.73); ν_{max}/cm^{-1} 3463w, 3374w and 3304w (NH_2), 3202w, 3142w (Ph CH), 2214m (C≡N), 1624m, 1605m, 1582m, 1566m, 1547s, 1499m, 1483m, 1450w, 1395w, 1306w, 1246m, 1178w, 1130w, 1069w, 1051w, 1028w, 995w, 897w, 856w, 839w, 818w, 752m; δ_H (300 MHz; DMSO-d_6) 11.14 (1H, br s, N*H*), 8.31 (1H, br s, N*H*Ph), 7.44 (2H, app d, *J* 5.7, Ph *H*-2 & 6), 7.16 (2H, app t, *J* 7.2, Ph *H*-3 & 5), 6.75 (1H, app t, *J* 7.2, Ph *H*-4), 6.25 (2H, br s, NH_2); δ_C (75 MHz; DMSO-d_6) 152.85 (br & w), 150.8 (br & w), 142.6, 128.4 (Ph *C*H), 119.0 (Ph *C*H),

116.0 (Ph *C*H), 115.2 (*C*≡N), 63.1 (br & w, *C*C≡N); δ_C (75 MHz; DEPT-135, DMSO-d_6) 128.4 (Ph *C*H), 119.0 (Ph *C*H), 116.0 (Ph *C*H); *m*/*z* (EI) 199 (M^+, 56%), 170 (11), 169 (12), 144 (16), 129 (4), 117 (6), 104 (4), 98 (6), 92 ($C_6H_6N^+$, 4), 77 ($C_6H_5^+$, 23), 67 (7), 66 (9), 51 (17).

4.31. 5-(*N*-Benzylamino)-3-chloroisothiazole-4-carbonitrile 33

To a stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **37** (500 mg, 2.80 mmol) in EtOH (20 mL) at ca. 0 °C, protected with a $CaCl_2$ drying tube, benzylamine (612 μL, 5.60 mmol) was added. The reaction mixture was allowed to warm to ca. 20 °C and stirred for 24 h until no starting material remained (TLC). The precipitate which formed was collected by filtration to afford the *title compound* **33** (627 mg, 90%) as colourless needles, mp 159.5–161.5 °C (from cyclohexane); λ_{max} (*t*-BuOMe)/nm 228 (log ε 2.93), 269 (3.08); ν_{max}/cm^{-1} 3245m (NH), 3123w, 3008w, 2862w, 2225m (C≡N), 1582s, 1479s, 1454m, 1363m, 1351m, 1339w, 1296m, 1224w, 1072w, 1026s, 991w, 958w, 923w, 858w, 828w, 781m, 756s, 701s; δ_H (300 MHz; $CDCl_3$) 7.44–7.32 (5H, m, Ph *H*), 6.84 (1H, br s, N*H*), 4.39 (2H, d, *J* 5.4, C*H*$_2$); δ_C (75 MHz; $CDCl_3$) 179.4, 148.2, 134.0, 129.1 (Ph *C*H), 128.8 (Ph *C*H), 128.0 (Ph *C*H), 112.6 (*C*≡N), 85.95 (*C*C≡N), 51.3 (*C*H$_2$); δ_C (75 MHz; DEPT-135, $CDCl_3$) 129.1 (Ph *C*H), 128.8 (Ph *C*H), 128.0 (Ph *C*H), 51.3 (*C*H$_2$); *m*/*z* (EI) 251 (M^++2, 13%), 249 (M^+, 34), 91 ($PhCH_2^+$, 100), 77 ($C_6H_5^+$, 10), 65 (53), 51 (12).

4.32. 3-Amino-5-(*N*-benzylamino)-1*H*-pyrazole-4-carbonitrile 50

Similar treatment of 5-(*N*-benzylamino)-3-chloroisothiazole-4-carbonitrile **33** (57 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the title compound **50** (45 mg, 92%) as a colourless powder, mp 142–143 °C (lit.,[87] 142 °C) (from EtOH); λ_{max} (*t*-BuOMe)/nm 236 (log ε 4.50), 250 inf (4.34), 294 inf (3.95), 336 inf (3.61); ν_{max}/cm^{-1} 3395w, 3335w, 3248w (NH), 3175w (Ar CH), 3129w (Ar CH), 2955w (Ar CH), 2922m (Ar CH), 2853w, 2205s (C≡N), 1612s, 1595m, 1560m, 1531m, 1499m, 1452m, 1416w, 1368w, 1348m, 1304w, 1248w, 1213w, 1142w, 1109w, 1080w, 1040w, 1028w, 984w, 804w, 754m, 721m; δ_H (300 MHz; DMSO-d_6) 10.68 (1H, s, N*H*), 7.28–7.19 (5H, m, PhC*H*), 6.30 (1H, s, N*H*), 5.73 (2H, s, N*H*$_2$), 4.24 (2H, s, C*H*$_2$); δ_C (75 MHz; DMSO-d_6) 155.7, 154.7, 141.3, 128.85 (Ph *C*H), 128.1 (Ph *C*H), 127.3 (Ph *C*H), 116.9 (*C*≡N), 55.7, 46.7; δ_C (75 MHz; DEPT-135, DMSO-d_6) 128.85 (Ph *C*H), 128.1 (Ph *C*H), 127.3 (Ph *C*H); *m*/*z* (EI) 213 (M^+, 6%), 149 (4), 123 (4), 106 (8), 98 (8), 91 ($PhCH_2^+$, 71), 83 (8), 77 ($C_6H_5^+$, 9), 65 (15), 57 (22).

4.33. 3-Amino-5-methoxy-1*H*-pyrazole-4-carbonitrile 51

A mixture of 3-amino-5-methoxyisothiazole-4-carbonitrile **34** (45 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at ca. 20 °C until no starting material remained (TLC) and then poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 1:1) gave 3-chloro-5-hydrazinoisothiazole-4-carbonitrile **31** (12 mg, 30%) as colourless needles, mp 151–152 °C (lit.,[49] 150 °C) (from cyclohexane), R_f (hexane/EtOAc, 1:1) 0.50; identical to an authentic sample. Further elution (EtOAc, 100%) gave the title compound **51** (32 mg, 65%) as colourless needles, mp 173–174 °C, (lit.,[91] 160–161 °C) (from pentane/EtOH); R_f (EtOAc) 0.60; λ_{max} (*t*-BuOMe)/nm 221 (log ε 2.72); ν_{max}/cm^{-1} 3414w and 3337w (NH_2), 3225w, 3115w, 3105w, 3024w, 2992w, 2951w, 2895w and 2812w (CH_3), 2210s (C≡N), 1634m, 1601w, 1568m, 1516s, 1458w, 1416m, 1368w, 1275w, 1196w, 1136w, 1105m, 1014w, 978w, 799m, 719m; δ_H (300 MHz; DMSO-d_6) 11.06 (1H, br s, N*H*), 6.37 (2H, br s, N*H*$_2$), 3.75 (3H, s, C*H*$_3$O); δ_C (75 MHz; DMSO-d_6) 162.7, 154.1, 115.4 (*C*≡N), 60.7 (*C*C≡N), 56.0 (*C*H$_3$O); δ_C (75 MHz; DEPT-135, DMSO-d_6) 56.0 (*C*H$_3$O); *m*/*z* (EI) 138 (M^+, 100%), 137 (M^+−1, 41), 123 (M^+−CH_3, 18), 109 (20), 93 (12), 81 (12), 67 (43), 66 (38).

4.34. 3-Chloro-5-hydrazinylisothiazole-4-carbonitrile 31 (via 5-phenoxyisothiazole 35)

A mixture of 3-chloro-5-phenoxyisothiazole-4-carbonitrile **35** (54 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at ca. 20 °C until no starting material remained (TLC) and then poured onto crushed ice (50 g) and extracted with DCM (3×50 mL). The organic extracts were combined and evaporated to afford the title compound (34 mg, 85%) as colourless needles, mp 151–152 °C (lit.,[49] 150 °C) (from cyclohexane), identical to that described above.

4.35. 3-Chloro-5-hydrazinylisothiazole-4-carbonitrile 31 (via 5-thiophenoxyisothiazole 36)

A mixture of 3-chloro-5-thiophenoxyisothiazole-4-carbonitrile **36** (58 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at ca. 20 °C until no starting material remained (TLC) and then poured onto crushed ice (50 g) and extracted with DCM (3×50 mL). The organic extracts were combined and evaporated to afford the title compound (36 mg, 90%) as colourless needles, mp 151–152 °C (lit.,[49] 150 °C) (from cyclohexane), identical to that described above.

4.36. 3-Chloro-5-hydrazinylisothiazole-4-carbonitrile 31 (via 3,5-dichloroisothiazole 37)

A mixture of 3,5-dichloroisothiazole-4-carbonitrile **37** (41 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at ca. 20 °C until no starting material remained (TLC) and then poured onto crushed ice (50 g) and extracted with DCM (3×50 mL). The organic extracts were combined and evaporated to afford the title compound (40 mg, 100%) as colourless needles, mp 151–152 °C (lit.,[49] 150 °C) (from cyclohexane), identical to that described above.

4.37. 3-Amino-5-phenyl-1*H*-pyrazole 59

A mixture of 3-chloro-5-phenylisothiazole **55** (45 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at ca. 20 °C until no starting material remained (TLC). The reaction mixture was then poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 7:3) gave the title compound **59** (26 mg, 70%) as colourless needles, mp 124–126 °C (lit.,[92] 125 °C) (from EtOH); R_f (hexane/EtOAc, 7: 3) 0.75; λ_{max} (*t*-BuOMe)/nm 206 (log ε 4.13) 222 inf (3.98), 254 inf (3.74); ν_{max}/cm^{-1} 3327w, 3219m (NH), 3042w (NH_2), 2938w (Ph CH), 1697m, 1649s, 1593s, 1562s, 1501s, 1435w, 1366m, 1281m, 1265m, 1113w, 1016m, 945w, 922w; δ_H (300 MHz; DMSO-d_6) 2 peaks missing, 7.64–7.26 (3H, m, Ph C*H*), 5.77 (1H, s); δ_C (75 MHz; DMSO-d_6) 153.0, 145.4, 132.0, 128.5 (Ph *C*H), 127.2 (Ph *C*H), 124.6 (Ph *C*H), 87.2 (pyrazole *C*-4); δ_C (75 MHz; DEPT-135, DMSO-d_6) 128.5 (Ph *C*H), 127.2 (Ph *C*H), 124.6 (Ph *C*H); *m*/*z* (EI) 159 (M^+, 17%), 130 (5), 116 (5), 103 (3), 77 ($C_6H_5^+$, 6), 74 (21), 58 (2).

4.38. Reaction of 4-bromo-3-chloro-5-phenylisothiazole 56 with anhydrous hydrazine (see Table 5)

A mixture of 4-bromo-3-chloro-5-phenylisothiazole **56** (63 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was heated to ca. 110 °C until no starting material remained (TLC). The reaction mixture was allowed to cool to ca. 20 °C, poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography

(hexane/EtOAc, 9:1), gave 3-chloro-5-phenylisothiazole **55** (9 mg, 20%) as colourless needles, mp 50–51 °C (lit.,[82] 50–51 °C) (from pentane), R_f (hexane/EtOAc, 9:1) 0.80; identical to an authentic sample. Further elution (hexane/EtOAc, 9:1) gave the 3-amino-4-bromo-5-phenylisothiazole **60** (32 mg, 55%) as pale yellow plates, mp 123–124 °C (lit.,[93] 126 °C) (from cyclohexane); R_f (hexane/EtOAc, 9:1) 0.63; λ_{max} (DCM)/nm 265 (log ε 4.33); ν_{max}/cm^{-1} 3446w (NH_2), 3286w, 3186w, 3171w, 3051w (Ph CH), 1623m, 1549w, 1498m, 1464w, 1444w, 1416m, 1333w, 1312w, 1080m, 1029w, 942w, 912w, 844s, 822w, 750s; δ_H (300 MHz; $CDCl_3$) 7.64–7.60 (2H, m, Ph C*H*), 7.51–7.46 (3H, m, Ph C*H*), 4.37 (2H, br s, NH_2); δ_C (75 MHz; $CDCl_3$) 162.05, 160.55, 130.4, 130.4 (Ph *C*H), 129.4 (Ph *C*H), 128.6 (Ph *C*H), 94.6 (*C*Br); δ_C (75 MHz; DEPT-135, $CDCl_3$) 130.4 (Ph *C*H), 129.4 (Ph *C*H), 128.6 (Ph *C*H); *m*/*z* (EI) 256 (M^++2, 100%), 254 (M^+, 99), 208 (5), 175 (M^+−Br, 6), 148 (8), 133 (31), 128 (39), 121 (13), 104 (5), 101 (7), 89 (28), 77 ($C_6H_5^+$, 16), 63 (9), 51 (19). Further elution (hexane-EtOAc, 9: 1) gave *4-bromo-3-hydrazinyl-5-phenylisothiazole* **61** (10 mg, 16%) as colourless needles, mp 135.5–137.5 °C (from cyclohexane); R_f (hexane/EtOAc, 9:1) 0.13; [Found C, 40.1; H, 2.9; N, 15.6. $C_9H_8BrN_3S$ requires C, 40.0; H, 3.0; N, 15.5%]; λ_{max} (DCM)/nm 263.3 (log ε 2.76); ν_{max}/cm^{-1} 3300m (NH), 3242m, 3205w, 3058w and 3026w (Ph CH), 1622w, 1559s, 1516s, 1447w, 1343m, 1168w, 1148w, 1080m, 1030m, 974w, 937w, 908w, 858m, 831w, 813w, 743s; δ_H (300 MHz; DMSO-d_6) 7.84 (1H, br s, N*H*), 7.65–7.58 (2H, m, Ph *H*), 7.58–7.50 (3H, m, Ph *H*), 4.72 (2H, br s, NH_2); δ_C (75 MHz; DMSO-d_6) 164.5, 159.0, 129.95 (Ph *C*H), 129.6 (Ph *C*), 129.2 (Ph *C*H), 127.9 (Ph *C*H), 92.5 (*C*Br); δ_C (75 MHz; DEPT-135, DMSO-d_6) 129.95 (Ph *C*H), 129.2 (Ph *C*H), 127.9 (Ph *C*H); *m*/*z* (EI) 271 (M^++2, 100%), 269 (M^+, 90), 242 (9), 240 (9), 208 (16), 206 (M^+−H_3N_2S, 16), 173 (6), 161 (24), 148 (8), 133 (19), 128 (41), 127 (55), 121 (28), 115 (7), 102 (8), 101 (10), 100 (10), 89 (25), 77 ($C_6H_5^+$, 28), 63 (10). Further elution (EtOAc, 100%), gave 3-amino-5-phenyl-1*H*-pyrazole **59** (2.5 mg, 6%) as colourless needles, mp 124–126 °C (lit.,[92] 125 °C) (from EtOH) identical to that described above.

4.39. Stability of 4-bromo-3-hydrazinyl-5-phenylisothiazole 61 (Table 6)

A mixture of 4-bromo-3-hydrazinyl-5-phenylisothiazole **61** and degassed DCM (1 mL) was stirred at ca. 20 °C under an argon atmosphere. After 3 d the reaction mixture was adsorbed onto silica. Chromatography (hexane/EtOAc, 9: 1) gave 3-amino-4-bromo-5-phenylisothiazole **60** (11 mg, 56%) as pale yellow plates, mp 123–124 °C (lit.,[93] 126 °C) (from cyclohexane) identical to that described above. Further elution (hexane/EtOAc, 9: 1) gave 3-amino-5-phenylisothiazole **62** (5.6 mg, 43%) as colourless needles, mp 190–192 °C (lit.,[93] 194 °C) (from cyclohexane); R_f (hexane/EtOAc, 9:1) 0.70; λ_{max} (DCM)/nm 264 (log ε 4.41); ν_{max}/cm^{-1} 3300w, 3240w, 3206w (NH_2), 3059w, 3024w (Ph CH), 1701w, 1622m, 1558s, 1518s, 1497m, 1462w, 1441w, 1422w, 1395w, 1342w, 1167w, 1080m, 1030w, 974w, 907w, 858m, 833w, 818w, 750s, 743s, 729w; δ_H (300 MHz; $CDCl_3$) 7.55–7.52 (2H, m, Ph C*H*), 7.42–7.40 (3H, m, Ph C*H*), 6.73 (1H, s, isothiazole *H*-4), 4.66 (2H, s, NH_2); δ_C (75 MHz; $CDCl_3$) 167.2, 165.1, 131.1, 130.3, 129.6 (Ph C*H*), 126.8 (Ph C*H*), 108.9; *m*/*z* (EI) 176 (M^+, 100%), 159 (2), 148 (2), 134 (5), 128 (47), 121 (5), 102 (10), 89 (10), 77 ($C_6H_5^+$, 12), 74 (16), 63 (5), 51 (8). Further elution (EtOAc, 100%) gave the starting 4-bromo-3-hydrazinyl-5-phenylisothiazole **61** identical to an authentic sample. Similar procedure was followed using an oxygen atmosphere.

4.40. Reaction of 4-bromo-3-hydrazinyl-5-phenylisothiazole 61 with anhydrous hydrazine (see Table 7)

A mixture of 4-bromo-3-hydrazinyl-5-phenylisothiazole **61** and anhydrous hydrazine (2 mL) was heated to ca. 110 °C until no starting material remained (TLC). The reaction mixture was poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 1; 1) gave the title compound **62** (16 mg, 39%) as colourless needles, mp 190–192 °C (lit.,[93] 194 °C) (from cyclohexane), identical to that described above. Further elution (EtOAc, 100%) gave 3-amino-5-phenyl-1*H*-pyrazole **59** (18 mg, 50%) as colourless needles, mp 124–126 °C (lit.,[92] 125 °C) (from EtOH) identical to that described above.

4.41. Reaction of 3-chloro-4,5-diphenylisothiazole 57 with anhydrous hydrazine (see Table 8)

A stirred mixture of 3-chloro-4,5-diphenylisothiazole **57** (50 mg, 0.185 mmol) and anhydrous hydrazine (2 mL) in a sealed tube, was introduced into a preheated Wood's metal bath at 150 °C and held at this temperature until no starting material remained (TLC). The mixture was allowed to cool to ca. 20 °C and poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic layer separated, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 9:1) gave 3-amino-4,5-diphenylisothiazole **63** (18 mg, 39%) as colourless needles, mp 130–131 °C, (lit.,[82] 130–131 °C) (from cyclohexane), R_f (hexane/EtOAc, 9:1) 0.60; identical to an authentic sample. Further elution (hexane/EtOAc 1:1) gave *3-hydrazinyl-4,5-diphenylisothiazole* **64** as colourless needles, mp 124.5–125.5 °C (from cyclohexane); R_f (hexane/EtOAc, 1:1) 0.50; [Found C, 67.45; H, 5.0; N, 15.75; $C_{15}H_{13}N_3S$ requires: C, 67.4; H, 4.9; N, 15.7%]; λ_{max} (DCM)/nm 230 (log ε 3.32), 265 (3.14); ν_{max}/cm^{-1} 3337w, 3294w, 3142w, 1600w, 1576w, 1557w, 1542w, 1495m, 1464w, 1438w, 1357w, 1272w, 1156w, 1080w, 1057w, 986w, 975w, 968w, 874w, 772m, 54s, 735m; δ_H (300 MHz; DMSO-d_6) 7.39–6.98 (10H, m, Ph C*H*), 6.98 (1H, s, N*H*), 4.77 (2H, s, NH_2); δ_C (75 MHz; DMSO-d_6) (1 peak missing) 167.0, 161.3, 132.9, 131.6, 130.8, 129.9, 129.8, 129.7, 128.8, 123.0; *m*/*z* (EI) 267 (M^+, 100%), 249 (55), 236 (9), 218 (18), 204 (10), 190 (9), 178 (17), 165 (15), 152 (7), 121 (26), 104 (5), 89 (9), 77 ($C_6H_5^+$, 27), 63 (6), 51 (16). Further elution (EtOAc, 100%) gave 3-amino-4,5-diphenyl-1*H*-pyrazole **65** as colourless needles, mp 144–145 °C (lit.,[94] 147–148 °C) (from EtOH); R_f (EtOAc) 0.60; λ_{max} (*t*-BuOMe)/nm 232 (log ε 3.83), 242 inf (3.81), 257 inf (3.79); ν_{max}/cm^{-1} 3360w, 3345w, 3252w, 3163w (NH_2), 2903w (Ph CH), 1603w, 1587w, 1568w, 1533w, 1520w, 1501m, 1476w, 1441w, 1425w, 1323w, 1312w, 1244w, 1180w, 1098w, 1072w, 1016m, 964w, 914w, 847w, 835w, 781m, 772m, 746m, 731m; δ_H (300 MHz; DMSO-d_6) 11.93 (1H, br s, N*H*), 7.35–7.13 (10H, m, Ph C*H*), 4.55 (2H, br s, NH_2); δ_C (75 MHz; DMSO-d_6) (3 peaks missing) 133.6, 129.1 (Ph *C*H), 128.4 (Ph *C*H), 128.2 (Ph *C*H), 127.35 (Ph *C*H), 127.1 (Ph *C*H), 125.6 (Ph *C*H), 103.4 (w & br); δ_C (75 MHz; DEPT-135, DMSO-d_6) 129.1 (Ph *C*H), 128.4 (Ph *C*H), 128.2 (Ph *C*H), 127.3 (Ph *C*H), 127.1 (Ph *C*H), 125.6 (Ph *C*H); *m*/*z* (EI) 235 (M^+, 100%), 218 (4), 206 (5), 190 (9), 178 (10), 165 (14), 152 (6), 139 (3), 128 (6), 117 (7), 104 (14), 89 (11), 77 ($C_6H_5^+$, 24), 63 (10), 51 (21).

4.42. 3,5-Diphenylisothiazole 66

A stirred mixture of 4-bromo-3,5-diphenylisothiazole **67** (73 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) in a sealed tube, was introduced into a preheated Wood's metal bath at 200 °C and was held at this temperature until no starting material remained (TLC). The reaction mixture was allowed to cool to ca. 20 °C and poured onto crushed ice (50 g) to afford the title compound **66** as a white precipitate, mp 80–81 °C (lit.,[82] 80–81 °C) (from pentane), identical to an authentic sample.

4.43. 4-Amino-3,5-diphenylpyrazole 70

A mixture of 4-amino-3,5-diphenylisothiazole **69** (50 mg, 0.2 mmol) and anhydrous hydrazine (2 mL) was stirred at ca. 150 °C

until no starting material remained (TLC). The reaction mixture was then allowed to cool to ca. 20 °C, poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 1:1) gave the title compound **70** (9.4 mg, 20%, based on recovered starting material) as colourless needles, mp 200–202 °C (lit.,[95] 208 °C) (from EtOH); R_f (hexane/EtOAc, 1: 1) 0.18; ν_{max}/cm^{-1} 3229w, 3211w, 3192w, 3055w, 2955w, 2924w, 2853w, 1730w, 1607m, 1587w, 1495m, 1458m, 1439m, 1364w, 1315w, 1294w, 1287w, 1221w, 1177m, 1074m, 1026m, 953s, 914m, 765s; δ_H (300 MHz; DMSO-d_6) 12.78 (1H, s, N*H*), 7.76–7.32 (10H, m, Ph C*H*), 4.0 (2H, s, NH_2); *m*/*z* (EI) 235 (M^+, 100%), 220 (8), 132 (17), 117 (6), 104 (81), 77 (50), 51 (19), identical to an authentic sample.

4.44. 5,5′-Diphenyl-1*H*,1′*H*-3,3′-bipyrazole-4,4′-dicarbonitrile 79

A mixture of 5,5′-diphenyl-3,3′-biisothiazole-4,4′-dicarbonitrile **78** (50 mg, 0.14 mmol) and anhydrous hydrazine (2 mL) was stirred at ca. 110 °C until no starting material remained (TLC). The reaction mixture was then allowed to cool to ca. 20 °C, poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 7:3) gave the *title compound* **79** (29.5 mg, 65%) as a pale yellow powder, mp >300 °C (from EtOH); R_f (hexane/EtOAc, 7:3) 0.18; λ_{max} (*t*-BuOMe)/nm 206 (log ε 4.43), 241 (4.32), 263 (4.32); ν_{max}/cm^{-1} 3191m, 3119w, 3026w (Ph CH), 2952w, 2924w, 2237s (C≡N), 1636w, 1559w, 1491w, 1475m, 1398w, 1368w, 1300w, 1279w, 1076m, 1039m, 1015m, 956s, 914w, 799m, 765m, 707m; δ_H (300 MHz; DMSO-d_6) 7.92–7.90 (4H, m, Ph C*H*), 7.66–7.59 (6H, m, Ph C*H*); δ_C (75 MHz; DMSO) 149.55, 146.5, 131.4 (Ph *C*H), 130.3 (Ph *C*H), 127.6 (Ph *C*H), 127.3 (Ph *C*), 115.5 (*C*≡N), 87.1 (*CC*≡N); *m*/*z* (EI) 336 (M^+, 60%), 307 (4), 280 (6), 251 (4), 194 (3), 177 (8), 149 (18), 127 (9), 104 (10), 89 (6), 77 ($C_6H_5^+$, 36), 64 (9), 57 (11) [Found: M^+, 336.1134. $C_{20}H_{12}N_6$ requires M, 336.1123].

4.45. Reaction of 3-chloro-5-phenylisothiazole 1 with methylhydrazine

A mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **1** (50 mg, 0.23 mmol) and methylhydrazine (1 mL) was stirred at ca. 20 °C until no starting material remained (TLC). The reaction mixture was then poured onto crushed ice (50 g) and extracted with EtOAc (3×50 mL). The organic layer was separated, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 1:1) gave *3-(1-methylhydrazinyl)-5-phenylisothiazole-4-carbonitrile* **83** (22 mg, 42%) as yellow needles, mp 129.5–131 °C (from cyclohexane); R_f (hexane/EtOAc, 1:1) 0.83; [Found C, 57.4; H, 4.2; N, 24.3. $C_{11}H_{10}N_4S$ requires C, 57.4; H, 4.4; N, 24.3%]; λ_{max} (DCM)/nm 275 (log ε 2.88), 332 (2.19); ν_{max}/cm^{-1} 3324w (NH), 3219w, 3061w (Ph CH), 2975w, 2940w, 2222m (C≡N), 1629m, 1536s, 1502m, 1457w, 1446w, 1430w, 1404m, 1386w, 1337w, 1272m, 1249w, 1195w, 1180w, 1120m, 1080w, 1041m, 1030m, 1001w, 968w, 933m, 915w, 855s, 820m, 755s, 722s; δ_H (300 MHz; $CDCl_3$) 7.73–7.70 (2H, m, Ph C*H*), 7.51–7.49 (3H, m, Ph C*H*), 4.02 (2H, br s, NH_2), 3.32 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 176.3, 168.9, 131.1 (Ph *C*H), 129.3 (Ph *C*H), 128.7 (Ph *C*), 127.5 (Ph *C*H), 115.2 (*C*≡N), 94.8 (*CC*≡N), 43.0 (*C*H_3); δ_C (75 MHz; DEPT-135, $CDCl_3$) 131.1 (Ph *C*H), 129.3 (Ph *C*H), 127.5 (Ph *C*H), 43.0 (*C*H_3); *m*/*z* (EI) 230 (M^+, 100%), 214 (22), 201 (4), 187 (11), 159 (5), 153 (8), 128 (15), 121 (60), 114 (5), 104 (12), 77 ($C_6H_5^+$, 20). Further elution (EtOAc, 100%) gave 3-amino-1-methyl-5-phenyl-1*H*-pyrazole-4-carbonitrile **84** (12 mg, 27%), as colourless needles, mp 158–159 °C (lit.,[78] 158 °C) (from EtOH); R_f (EtOAc) 0.55; [Found C, 66.7; H, 5.1; N, 28.3. $C_{11}H_{10}N_4$ requires C, 66.65; H, 5.1; N, 28.3%]; λ_{max} (EtOAc)/nm 252 (log ε 2.95); ν_{max}/cm^{-1} 3381m, 3311w (NH_2), 3213w (NH), 3034w (Ph CH), 2946w, 2220m (C≡N), 1638m, 1557m, 1533m, 1499m, 1479w, 1448w, 1428w, 1396w, 1314w, 1285w, 1248w, 1153w, 1078w, 1030w, 1002w, 931w, 896w, 854w, 779m, 771m, 741w, 715w, 700s; δ_H (300 MHz; $CDCl_3$) 7.52–7.43 (5H, m, Ph C*H*), 4.07 (2H, s, NH_2), 3.68 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 155.9, 148.0, 130.1 (Ph *C*H), 129.1 (Ph *C*H), 128.8 (Ph *C*H), 126.9 (Ph *C*), 114.35 (*C*≡N), 79.1 (*CC*≡N), 37.2 (*C*H_3); δ_C (75 MHz; DEPT-135, $CDCl_3$) 130.1 (Ph *C*H), 129.1 (Ph *C*H), 128.8 (Ph *C*H); *m*/*z* (EI) 198 (M^+, 100%), 183 (1), 170 (5), 155 (9), 143 (2), 128 (17), 115 (2), 101 (5), 88 (2), 77 ($C_6H_5^+$, 15), 63 (3), 51 (9).

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References and notes

1. Mulhall, J. *Br. J. Urol.* **1997**, *79*, 363.
2. Rainer, G.; Kruger, U.; Klemm, K. *Arzneim. -Forsch.* **1981**, *31*, 649.
3. Vinge, E.; Bjorkman, S. B. *Acta Pharmacol. Toxicol.* **1986**, *59*, 165.
4. Kameyama, T.; Ukai, M.; Nabeshima, T. *Chem. Pharm. Bull.* **1978**, *26*, 3265.
5. Naito, T.; Yoshikawa, T.; Kitahara, S.; Aoki, N. *Chem. Pharm. Bull.* **1969**, *17*, 1467.
6. Heijnen, H.; Geuze, H. *Histochemistry* **1977**, *54*, 39.
7. Jungheim, L. N.; Sigmund, S. K.; Fisher, J. W. *Tetrahedron Lett.* **1987**, *28*, 285.
8. Elguero, J. (eds. in Chief: Katritzky, A. R.; Rees, C. W.). In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 5, Chapter 4. 04, p 167.
9. Elguero, J. (eds. in Chief: Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.). In *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Pergamon: Oxford, 1996; Vol. 3, Chapter 3.01, p 1.
10. Yet, L. (eds. in Chief: Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K.). In *Comprehensive Heterocyclic Chemistry III*; Joule, J. A., Ed.; Elsevier: Oxford, 2008; Vol. 4, Chapter 4.01, p 1.
11. Stanovnik, B.; Svete, J. In *Pyrazoles*; Neier, R., Ed.; Science of Synthesis Product Class 1; Georg Thieme Verlag: Stuttgart, 2002; Vol. 12, p 15.
12. Christoforou, I. C.; Koutentis, P. A. *Org. Biomol. Chem.* **2006**, *4*, 3681.
13. Dornow, A.; Schleese, E. *Chem. Ber.* **1958**, *91*, 1830.
14. Minkin, V. I.; Garnovskii, A. D.; Elguero, J.; Katritzky, A. R.; Denisko, O. V. *Adv. Heterocycl. Chem.* **2000**, *76*, 157.
15. Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic: New York, NY, 1976; p 55.
16. Chenon, M. T.; Coupry, C.; Grant, D. M.; Pugmire, R. J. *J. Org. Chem.* **1977**, *42*, 659.
17. Elguero, J.; Fruchier, A.; Pellegrin, V. *J. Chem. Soc., Chem. Commun.* **1981**, 1207.
18. Claisen, L. *Chem. Ber.* **1909**, *42*, 59.
19. Schöttle, J. *Chem. Ber.* **1912**, *45*, 2340.
20. Cusmano, S. *Gazz. Chim. Ital.* **1939**, *69*, 594.
21. Cusmano, S. *Gazz. Chim. Ital.* **1940**, *70*, 86.
22. Cusmano, S. *Gazz. Chim. Ital.* **1940**, *70*, 227.
23. Cusmano, S. *Gazz. Chim. Ital.* **1940**, *70*, 235.
24. Cusmano, S. *Gazz. Chim. Ital.* **1940**, *70*, 240.
25. Bell, F. *J. Chem. Soc.* **1941**, 285.
26. Musante, C. *Gazz. Chim. Ital.* **1942**, *72*, 537.
27. Musante, C. *Gazz. Chim. Ital.* **1943**, *73*, 355.
28. Gardner, T. S.; Smith, F. A.; Wenis, E.; Lee, J. *J. Org. Chem.* **1956**, *21*, 530.
29. Musante, C.; Fatutta, S. *Gazz. Chim. Ital.* **1958**, *88*, 879.
30. Fatutta, S. *Gazz. Chim. Ital.* **1959**, *89*, 964.
31. Adembri, G.; Camparini, A.; Ponticelli, F.; Tedeschi, P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 971.
32. Adembri, G.; Camparini, A.; Donati, D.; Ponticelli, F.; Tedeschi, P. *Tetrahedron Lett.* **1978**, *19*, 4439.
33. Donati, D.; Fusi, S.; Ponticelli, F. *J. Heterocycl. Chem.* **1998**, *35*, 109.
34. Sviridov, S. I.; Vasil'ev, A. A.; Shorshnev, S. V. *Tetrahedron* **2007**, *63*, 12195.
35. Musante, C.; Stener, A. *Gazz. Chim. Ital.* **1959**, *89*, 1579.
36. Alberola, A.; Antolín, L. F.; Cuadrado, P.; González, A. M.; Laguna, M. A.; Pulido, F. J. *Synthesis* **1988**, 203.
37. Zelenin, K. N.; Lagoda, I. V. *Russ. J. Gen. Chem.* **2000**, *70*, 1887.
38. Shaw, G. *J. Chem. Soc.* **1952**, 3428.
39. Ponzio, G.; Carta-Satta, G. *Gazz. Chim. Ital.* **1930**, *60*, 150.
40. Boulton, A. J.; Roe, D. E.; Tsoungas, P. G. *Gazz. Chim. Ital.* **1981**, *111*, 167.
41. Knorr, L.; Reuter, B. *Chem. Ber.* **1894**, *27*, 1169.
42. Landesberg, J. M.; Olofson, R. A. *Tetrahedron* **1966**, *22*, 2135.
43. Sykes, P.; Ullah, H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2305.
44. Hassan, M. E.; Magraby, M. A.; Aziz, M. A. *Tetrahedron* **1985**, *41*, 1885.
45. Wolf, J.; Schulze, B. *Adv. Heterocycl. Chem.* **2007**, *94*, 215.

46. Fürstenwerth, H. U.S. Patent 4,892,958, 1990.
47. Bigelow, L. A.; Eatough, H. *Org. Synth.* **1941**, *1*, 80.
48. Adams, A.; Slack, R. *J. Chem. Soc.* **1959**, 3061.
49. Hatchard, W. R. *J. Org. Chem.* **1964**, *29*, 660.
50. Christoforou, I. C.; Koutentis, P. A.; Rees, C. W. *Org. Biomol. Chem.* **2003**, *1*, 2900.
51. Caton, M. P. L.; Martin, G. C. J.; Pain, D. L. *J. Chem. Soc. C (Org.)* **1971**, 776.
52. Lipnicka, U.; Machon, Z. *Acta Pol. Pharm.* **1997**, *54*, 207.
53. Krebs, H.-D. *Aust. J. Chem.* **1989**, *42*, 1291.
54. Joos, A.; Wirtz, W. U.S. Patent 3,657,261, 1972.
55. Davis, M.; Gordon, J. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 638.
56. Graubaum, H.; Lutze, G.; Ramm, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *84*, 83.
57. Acheson, R. M.; Jefford, C. W. *J. Chem. Soc.* **1956**, 2676.
58. Guha, P. C.; Mukherji, S. P. *Quart. J. Indian Inst. Sci., Sect. A* **1946**, *9*, 70.
59. Druey, J. CIBA. U.S. Patent 2,484,785, 1948.
60. Furst, A.; Berlo, R. C.; Hooton, S. *Chem. Rev.* **1965**, *65*, 51.
61. Busch, M.; Schulz, K. *Chem. Ber.* **1929**, *62*, 1458.
62. Chattaway, F. D.; Aldridge, M. *J. Chem. Soc., Trans.* **1911**, *99*, 404.
63. Mangia, M. T. L.; Pelizzi, G. *Gazz. Chim. Ital.* **1976**, *106*, 769.
64. Lipnicka, U.; Jasztold-Howorko, I. *Sci. Pharm.* **2004**, *74*, 275.
65. Ueda, T.; Shibata, Y.; Sakakibara, J. *J. Heterocycl. Chem.* **1986**, *23*, 1773.
66. Ueda, T.; Shibata, Y.; Kato, Y.; Sakakibara, J. *Tetrahedron* **1987**, *43*, 3917.
67. Fomum, Z. T.; Landor, S. R.; Landor, P. D.; Mpango, G. W. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2997.
68. Liang, C.; Ma, T.; Cooperwood, J. S.; Du, J.; Chu, C. K. *Carbohydr. Res.* **1997**, *303*, 33.
69. Ephraim, F.; Piotrowski, H. *Chem. Ber.* **1911**, *44*, 386.
70. Pain, D. L.; Peart, B. J.; Wooldridge, K. R. H. (eds. in Chief: Katritzky, A. R.; Rees C. W.). In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 6, Chapter 4.17, p 131.
71. Chapman, R. F.; Peart, B. J. (eds. in Chief: Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.). In *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Pergamon: Oxford, 1996; Vol. 3, Chapter 3.05, p 319.
72. Lovas, F. J.; Suenram, R. D.; Stevens, W. J. *J. Mol. Spectrosc.* **1983**, *100*, 313.
73. van der Plas, H. C. *Adv. Heterocycl. Chem.* **1999**, *74*, 9.
74. van der Plas, H. C. *Adv. Heterocycl. Chem.* **1999**, *74*, 87.
75. Joshi, N. S.; Karale, B. K.; Bhirud, S. B.; Gill, C. H. *J. Heterocycl. Chem.* **2004**, *41*, 541.
76. Patel, M.; Rodgers, J. D.; McHugh, R. J.; Johnson, B. L.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Ko, S. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3217.
77. Straub, A.; Stasch, J.-P.; Alonso-Alija, C.; Benet-Buchholz, J.; Ducke, B.; Feurer, A.; Fürstner, C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 781.
78. Peshkar, H. *Pharm. Zentralhalle* **1968**, *107*, 348.
79. Southwick, P. L.; Dhawan, B. *J. Heterocycl. Chem.* **1975**, *12*, 1199.
80. Lemieux, R. U.; Micetich, R. G. U.S. Patent 3,311,611, 1965.
81. Cutrì, C. C. C.; Garozzo, A.; Siracusa, M. A.; Sarvà, M. C.; Castro, A.; Geremia, E.; Pinizzotto, M. R.; Guerrera, F. *Bioorg. Med. Chem.* **1999**, *7*, 225.
82. Christoforou, I. C.; Koutentis, P. A. *Org. Biomol. Chem.* **2007**, *5*, 1381.
83. Sprio, V.; Fabra, J. *Gazz. Chim. Ital.* **1956**, *86*, 1059.
84. Yoshinori, T.; Yoshiki, N.; Shinya, K.; Akira, A. *Heterocycles* **1987**, *26*, 613.
85. Traxler, P.; Bold, G.; Frei, J.; Lang, M.; Lydon, N.; Mett, H.; Buchdunger, E.; Meyer, T.; Mueller, M.; Furet, P. *J. Med. Chem.* **1997**, *40*, 3601.
86. Zhang, X.-H.; Weng, L.-H.; Ji, G.-Y. *J. Chem. Crystallogr.* **2000**, *30*, 789.
87. Kobayashi, S. *Chem. Pharm. Bull.* **1973**, *21*, 941.
88. Middleton, W. J.; Engelhardt, V. A. *J. Am. Chem. Soc.* **1958**, *80*, 2822.
89. Wellcome, B. U.S. Patent 2,759,949, 1955.
90. Yoshinori, T.; Yasumasa, H.; Mayumi, H.; Akira, H. *J. Heterocycl. Chem.* **1990**, *27*, 775.
91. Anderson, J. D.; Dalley, K. N.; Revankar, G. R.; Robins, R. K. *J. Heterocycl. Chem.* **1986**, *23*, 1869.
92. Seidel, O. *J. Prakt. Chem.* **1898**, *58*, 129.
93. Goerdeler, J.; Mittler, W. *Chem. Ber.* **1963**, *96*, 944.
94. Alberti, C. *Gazz. Chim. Ital.* **1947**, *77*, 398.
95. Ruccia, M. *Ann. Chim.* **1959**, *49*, 720.