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Reinvestigating the Reaction of 1*H*-Pyrazol-5-amines with 4,5-Dichloro-1,2,3-dithiazolium Chloride: A Route to Pyrazolo[3,4-*c*]isothiazoles and Pyrazolo[3,4-*d*]thiazoles†

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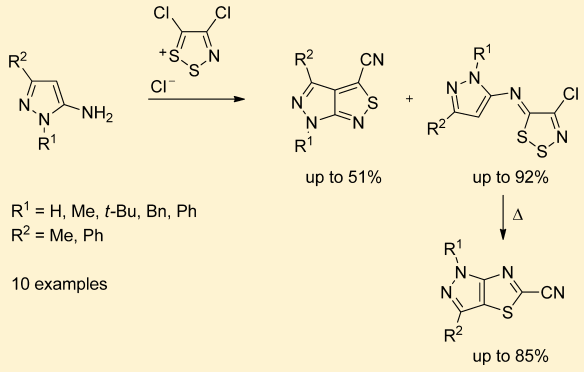
Supporting Information

ABSTRACT: The reaction of Appel salt **1** with 1*H*-pyrazol-5-amines **2** gives main products *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1*H*-pyrazol-5-amines **3**, and 6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitriles **5**, together with several minor side products. When the pyrazoles are N-1 methylated, the product ratio **3**:**5** can be modified by adjusting the pH of the reaction medium: acidic conditions favor formation of the dithiazolylidenes **3**, while basic conditions favor formation of pyrazolo[3,4-*c*]isothiazoles **5**. Furthermore, thermolysis of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1*H*-pyrazol-5-amines **3** gives 1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitriles **4**. Single crystal X-ray crystallography supports the structure of 4,6-dimethyl-6*H*-pyrazolo-[3,4-*c*]isothiazole-3-carbonitrile (**5a**) and helps resolve a previous incorrect structural assignment of 1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitriles **4**.



1. INTRODUCTION

Monocylic and benzo-fused thiazoles are important compounds, and their synthesis, chemistry, and applications have been extensively reviewed.[1] Less well studied are azole-condensed thiazoles;[2] nevertheless, several analogues show diverse bioactivity, while others are useful in the material sciences. For example, 4*H*-pyrrolo[2,3-*d*]thiazoles, 4*H*-pyrrolo-[3,2-*d*]thiazoles, 1*H*-pyrazolo[3,4-*d*]thiazoles, and 1*H*-pyrazolo-[4,3-*d*]thiazoles can modulate or inhibit various protein kinases, which are important in cancer therapy.[3] Furthermore, azole-fused thiazoles can influence the progress of neurological diseases such as schizophrenia or Alzheimer's disease: 4*H*-Pyrrolo[2,3-*d*]thiazoles and 4*H*-pyrrolo[3,2-*d*]thiazoles can inhibit D-amino acid oxidase,[4] while 1*H*-pyrazolo[3,4-*d*]-thiazoles and 1*H*-pyrazolo[4,3-*d*]thiazoles can modulate the mGluR4 receptor activity (Figure 1).[5] 4*H*-Pyrrolo[2,3-*d*]-thiazoles and 4*H*-pyrrolo[3,2-*d*]thiazoles can also act as anti-inflammatory agents (e.g., as cannabinoid hCB2 receptor agonists)[6a] and as inhibitors of MCP-1,[6b] or show antiallergic activity (e.g., as modulators of $CRTH_2$) (Figure 1).[7]

In the material sciences, thiazolo[5,4-*d*]thiazoles have been incorporated into donor/acceptor polymers or oligomers for use in organic semiconductors[8] and are components of silver halide photographic materials.[9] Despite their broad applications and unlike the 6−5 fused thiazoloheteroarenes,[1e−g,10] the synthesis of condensed 5−5 thiazoles via construction of the thiazole ring has not been extensively explored.[2]

Many syntheses for benzothiazoles, the most common 6−5 fused thiazole, focus on the preparation of the thiazole ring,[1a,b,d−g] and a mechanistically interesting and efficient

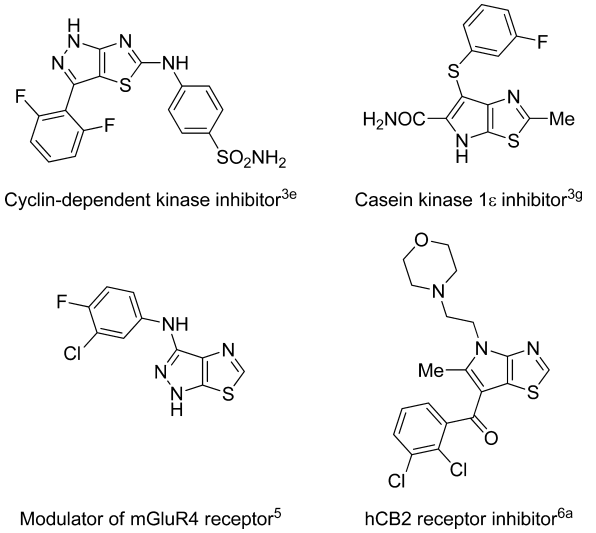


Figure 1. Representative structures of some biologically active azole-fused thiazoles.

route to benzothiazole-2-carbonitriles, discovered and developed by Rees,[11] involves thermolysis of *N*-(dithiazolylidene)-anilines.[12] Recently, an addition of the nucleophile, ring-opening, and ring closure (ANRORC)[13] mediated ring transformation of *N*-(dithiazolylidene)heteroazinamines[14] pro-

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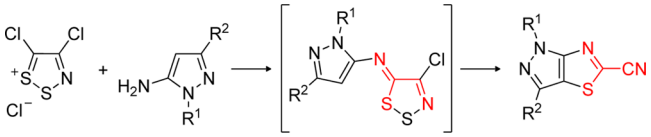
vided an efficient route to heteroazine-fused thiazole-2-carbonitriles.[15] Interestingly, while several *N*-(dithiazolylidene)-heterolamines are known,[16] only one report of their transformation into fused 5−5 thiazoles exists: L'abbé et al.[17] claimed the reaction of 4,5-dichloro-1,2,3-dithiazolium chloride (**1**) (Appel salt)[12] with 1*H*-pyrazol-5-amines **2** gave 1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitriles **4** via the in situ formation of the *N*-(dithiazolylidene)pyrazolamines **3** (Scheme 1).

Scheme 1. Reaction of Appel Salt 1 with 1,3-Disubstituted 1*H*-Pyrazol-5-amines 2 To Give 1*H*-Pyrazolo[3,4-*d*]thiazoles 4 (R^1, R^2 = Me, Ph)[17]

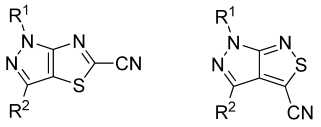


1 **2** **3** **4**

While the structure assignment for 1*H*-pyrazolo[3,4-*d*]-thiazoles **4** was presumably influenced by the known transformation of *N*-(dithiazolylidene)anilines into benzothiazoles,[11] we considered the spectral data provided to be inconclusive. In addition, the typical ring transformation of *N*-(dithiazolylidene)anilines into thiazoles requires thermolytic temperatures, and to the best of our knowledge, there are no reports of room temperature transformations. As such, the reported in situ transformation to give 1*H*-pyrazolo[3,4-*d*]thiazoles **4** was unique.

Furthermore, 1*H*-pyrazol-5-amines **2** are ambident nucleophiles,[18] which can react with electrophiles via the C-4 ring carbon (enaminic attack) as well as via the exocyclic amino group (normal attack). As such, we hypothesized that 6*H*-pyrazolo[3,4-*c*]isothiazoles **5** may have been formed as well as, or instead of, the proposed 1*H*-pyrazolo[3,4-*d*]thiazoles **4**. These two bicyclic hetarenes would have similar spectroscopic properties, making a conclusive assignment difficult.

via normal attack *via* enaminic attack



4 **5**

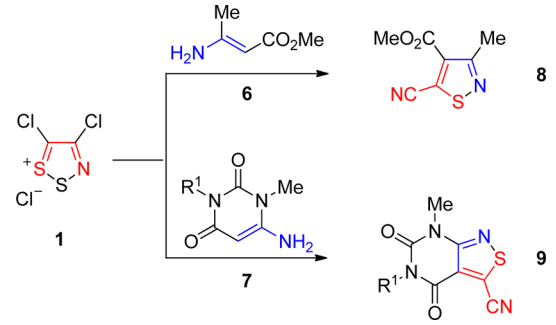
Reactions reported by Rees[19] and Kim,[20] in which primary enamines such as methyl 3-aminocrotonate (**6**) and 6-amino-1,3-dialkyluracils **7** react with Appel salt **1** to give 5-cyano-3-methylisothiazole-4-carboxylate **8** and 5,7-dialkyl-4,6-dioxo-4,5,6,7-tetrahydroisothiazolo[3,4-*d*]pyrimidine-3-carbonitriles **9**, respectively (Scheme 2), support our hypothesis.

Herein, we describe our reinvestigation of the reaction of Appel salt **1** with 1*H*-pyrazol-5-amines **2**, which gives 6*H*-pyrazolo[3,4-*c*]isothiazoles **5**, previously misassigned as 1*H*-pyrazolo[3,4-*d*]thiazoles **4**,[17] and *N*-(dithiazolylidene)-pyrazolamines **3**, which on thermolysis give 1*H*-pyrazolo[3,4-*d*]thiazoles **4**.

2. RESULTS AND DISCUSSION

2.1. Reaction of Appel Salt 1 with 1*H*-Pyrazol-5-amines 2. Adding a solution of 1,3-dimethyl-1*H*-pyrazol-5-amine (**2a**) (1 equiv) and lutidine (2 equiv) in DCM (20 mL)

Scheme 2. Reactions of Enamines 6 and 7 with Appel Salt 1 To Give Isothiazole-5-carbonitriles 8 and 9, Respectively



to a stirred suspension of Appel salt **1** (1.0 g, 1 equiv) in DCM (20 mL) under argon at ca. 20 °C followed by stirring for 1 h was reported to give 1,3-dimethyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitrile (**4a**) in 81% yield.[17] In our hands, however, the reaction gave a complex mixture from which we isolated five products: 4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5a**), *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1,3-dimethyl-1*H*-pyrazol-5-amine (**3a**), 5-amino-1,3-dimethyl-1*H*-pyrazole-4-carbothioyl cyanide (**10**), (3*Z*,3′*Z*)-*N*′,*N*″-trisulfanediylbis(4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbimidoyl chloride) (**11**), and (*Z*)-*N*-{[(*Z*)-1-(5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)-2-chloro-2-[(*Z*)-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino]vinyl]disulfanyl}-4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbimidoyl chloride (**12**) in 12, 5, 4, 12, and 13% yields, respectively (Scheme 3).

4,6-Dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5a**) was isolated as colorless needles, mp 102−106 °C (from *c*-hexane). Microanalysis and mass spectrometry supported the formula $C_7H_6N_4S$. The NMR and IR spectroscopic data matched that reported for the isomeric 1,3-dimethyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitrile (**4a**);[17] however, single crystal X-ray diffraction studies (Supporting Information, Figure S1) identified the structure to be the fused isothiazole **5a** and not the fused thiazole **4a** as previously reported.

The *N*-(dithiazolylidene)pyrazolamine **3a** was obtained as yellow prisms, mp 154−156 °C (from *c*-hexane), and was stable at room temperature; no decomposition was observed during a hot recrystallization. Differential scanning calorimetry (DSC) of *N*-(dithiazolylidene)pyrazolamine **3a** gave a decomposition with an onset point at 158.2 °C, and its thermolysis on a quantitative scale (0.1 mmol) under argon atmosphere at ca. 170 °C gave S_8 (78%), traces (by TLC) of an unidentified side product, and 1,3-dimethyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitrile (**4a**) (77%) (see Table 2, entry 1). The spectroscopic data collected for pyrazolo[3,4-*d*]thiazole-5-carbonitrile **4a** prepared in this manner differed significantly from that reported in the literature.[17] With the single crystal X-ray diffraction study of the above fused isothiazole **5a**, we therefore concluded that the earlier structural assignment for the fused thiazole **4a** was incorrect.

5-Amino-1,3-dimethyl-1*H*-pyrazole-4-carbothioyl cyanide (**10**) was obtained as orange plates, mp 212−213 °C (from $CHCl_3$). Microanalysis and mass spectrometry supported the formula $C_7H_8N_4S$. The ^{1}H NMR spectrum showed the presence of two methyl groups, the absence of the pyrazole H-4 resonance, and the presence of a D_2O exchangeable NH_2 resonance at δ_H 7.23 ppm, which was further supported by IR spectroscopy ν(N−H) 3339 cm^{-1}. In addition to the two Me

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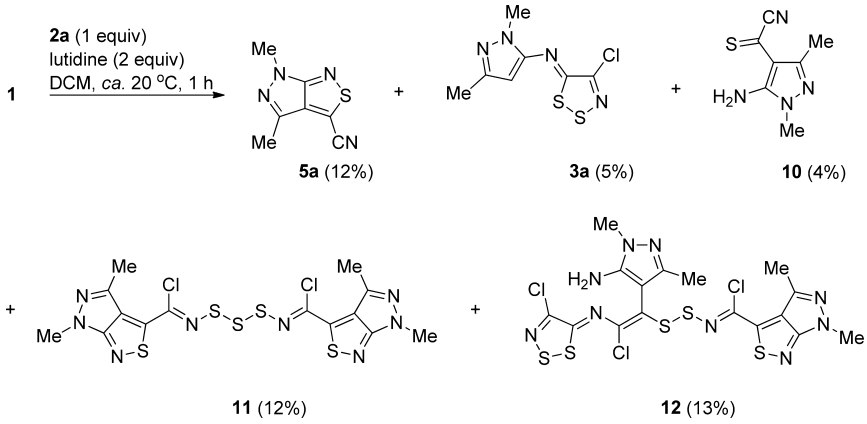
Scheme 3. Reaction of Appel Salt 1 with 1,3-Dimethyl-1*H*-pyrazol-5-amine (2a)



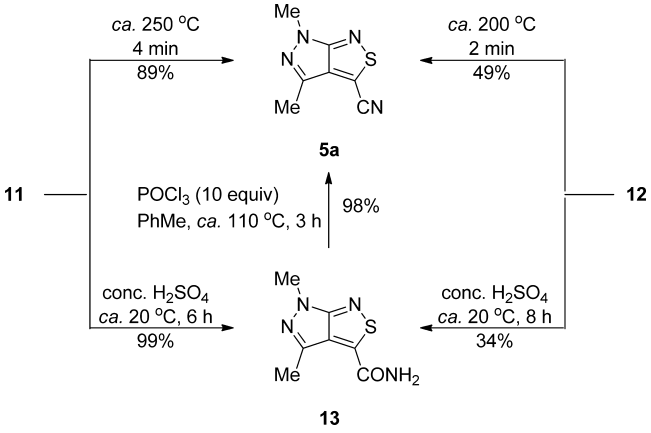
resonances, the ^{13}C NMR data showed the presence of five quaternary carbon resonances, one of which fitted for a nitrile at δ_C 116.2 ppm, as supported also by the FTIR stretching frequency at ν(C≡N) 2226 cm^{-1}. The structural assignment of compound **10** is tentative.

(3*Z*,3′*Z*)-*N*′,*N*″-3-Trisulfanediylbis(4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbimidoyl chloride) (**11**) was obtained as yellow needles, mp 201−208 °C (from DCE). Microanalysis and mass spectrometry tentatively supported the formula $C_{14}H_{12}Cl_2N_8S_5$, which fitted for two molecules of either fused pyrazoles **4a** or **5a** and S_3Cl_2. Interestingly, FTIR spectroscopy showed an absence of amino or cyano stretching frequencies. ^1H and ^{13}C NMR spectroscopy also supported the presence of four high-field quaternary signals corresponding to at least two dimethylpyrazoles. The absence of the H-4 pyrazole resonance in the ^1H NMR suggested the pyrazoles units have undergone substitution at the C-4 position; this was also supported by the ^{13}C NMR data. No resonances were visible in either of the ^{13}C NMR data that corresponded to the presence of *sp*-hybridized carbons, further supporting the absence of nitrile groups. On the basis of the above data, we suspected that a symmetrical trisulfur dichloride adduct of either fused pyrazole **4a** or **5a** had formed.

(*Z*)-*N*-{[(*Z*)-1-(5-Amino-1,3-dimethyl-1*H*-pyrazol-4-yl)-2-chloro-2-[(*Z*)-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino]-vinyl]disulfanyl}-4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbimidoyl chloride (**12**) was obtained as red needles, mp 143−145 °C (from *n*-pentane/DCM). Microanalysis and mass spectrometry tentatively supported the formula $C_{16}H_{14}Cl_3N_9S_5$. FTIR spectroscopy showed the presence of amino stretching frequencies ν(N−H) 3327w and 3196w cm^{-1}, which was also supported by a broad signal in the ^1H NMR spectrum at δ_H 3.77 ppm that integrated for two hydrogens and was D_2O exchangeable. The ^1H and ^{13}C NMR spectra also indicated the presence of four methyl groups, suggesting the presence of at least two dimethylpyrazole units.

On the basis of the above spectroscopic data, we were unable to confidently assign structures for side products **11** and **12**. As such, we attempted to elucidate further information on these products by investigating their stability toward heat or acid: heating pure samples of side products **11** and **12** gave 6*H*-pyrazolo[3,4-*c*]isothiazole **5a** (89 and 48%, respectively), while treating them with concd H_2SO_4 at ca. 20 °C gave carboxamide **13** (99 and 34%, respectively), dehydration of which using $POCl_3$ gave carbonitrile **5a** in 98% (Scheme 4).

Scheme 4. Behavior of Trisulfide 11 and Disulfide 12 under Thermal or Acidic Conditions



The data from these studies confirmed that the side products were composed of pyrazolo[2,3-*c*]isothiazoles or their possible intermediates. To resolve their structures conclusively, single crystals of both side products **11** and **12** were grown, and the structures were solved by single crystal X-ray crystallography (Supporting Information, Figures S2 and S3, respectively).

2.2. Optimization of the Reaction. Having identified the major products from the reaction of 1,3-dimethyl-1*H*-pyrazol-5-amine (**2a**) with Appel salt **1**, we investigated the influence of time and mode of reagent addition on the reaction. As shown above (section 2.1.), when a solution of pyrazol-5-amine **2a** in DCM was mixed with lutidine before the addition of Appel salt **1** and then stirred for 1−3 h, the reaction mixture was complex. Nevertheless, allowing the reaction to stir for longer (6−15 h) provided a significantly simpler reaction mixture (by TLC), and only 6*H*-pyrazolo[3,4-*c*]isothiazole **5a** could be isolated, although in a moderate 52% yield (Scheme 5, Conditions A). Alternatively, if the pyrazol-5-amine **2a** was left stirring with Appel salt **1** for 12 h before the addition of base, then *N*-(dithiazolylidene)pyrazolamine **3a** was isolated as the major product in 44% yield, together with a small quantity of pyrazoloisothiazole **5a** (14%). This result alerted us to the effect the amine base had on the yield of the *N*-(dithiazolylidene)pyrazolamine **3a**. Because pyrazol-5-amine **2a** itself can act as a base (e.g., 1-methyl-1*H*-pyrazol-5-amine has a pK_a of 9.77),[21] we carried out the reaction under nonbasic conditions by preparing the HCl salt of the pyrazolamine: adding Appel salt **1** to a suspension of pyrazolamine hydrochloride **2a**·**HCl** in

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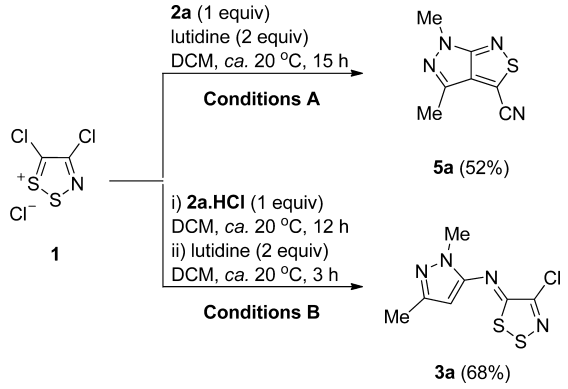
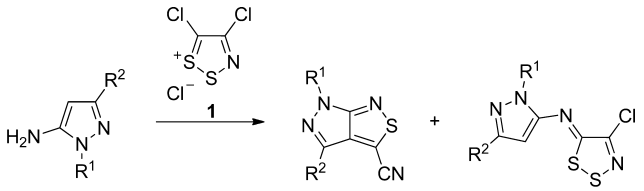
Scheme 5. Reaction of Appel Salt 1 with Pyrazol-5-amine 2a under Basic and Acidic Conditions



DCM or to a solution of pyrazolamine **2a** in DCM purged with HCl (g) led to the formation of *N*-(dithiazolylidene)-pyrazolamine **3a** in 68 and 69% yields, respectively (Scheme 5, Conditions B).

With these partially optimized conditions in hand, we screened the reaction of Appel salt **1** with a series of pyrazol-5-amines **2a–i** (Table 1). With 1-unsubstituted 1*H*-pyrazol-

Table 1. Reaction of Appel Salt 1 with Pyrazol-5-amines 2 (1 equiv) in DCM at ca. 20 °C



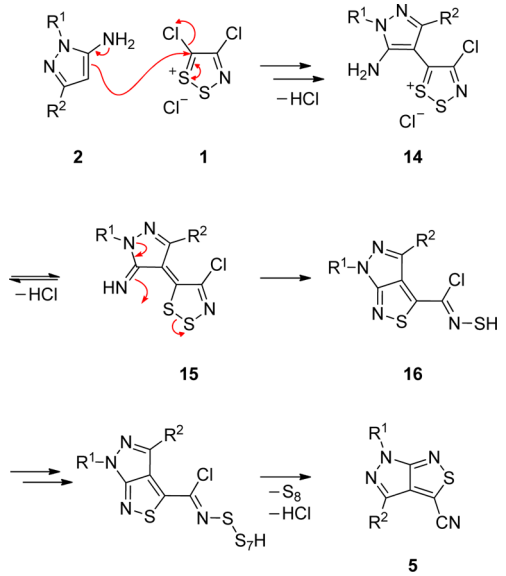
			yields (%)			
entry	R^1	R^2	Conditions A[a]		Conditions B[b]	
1	Me	Me	**5a** (51)	**3a** (0)	**5a** (1)	**3a** (70)
2	H	Me	**5b** (4)	**3b** (65)	**5b** (0)	**3b** (74)
3	H	Ph	**5c** (7)	**3c** (58)	**5c** (0)	**3c** (92)
4	Me	Ph	**5d** (45)	**3d** (0)	**5d** (5)	**3d** (73)
5	Bn	Me	**5e** (47)	**3e** (0)	**5e** (29)[c]	**3e** (17)[c]
6	Bn	Ph	**5f** (41)	**3f** (0)	**5f** (9)	**3f** (55)
7	*t*Bu	Me	**5g** (39)	**3g** (0)	**5g** (21)	**3g** (0)
8	*t*Bu	Ph	**5h** (38)	**3h** (0)	**5h** (37)	**3h** (0)
9	Ph	Me	**5i** (36)	**3i** (0)	**5i** (6)	**3i** (22)
10	Ph	Ph	**5j** (34)	**3j** (0)	**5j** (19)	**3j** (9)

[a]Conditions A: (i) DCM, lutidine (2 equiv), ca. 20 °C, 15 h. [b]Conditions B: (i) DCM, HCl (g), ca. 20 °C, 12 h; (ii) lutidine (2 equiv), ca. 20 °C, 3 h. [c]No HCl (g) was used.

amines **2b** and **2c**, regardless of which conditions were used, the major products were *N*-(dithiazolylidene)pyrazolamines **3b** and **3c**, while isothiazoles **5b** and **5c** were observed in very low yields (Table 1, entries 2 and 3). The reactions of Appel salt **1** with 1-methyl-3-phenyl-1*H*-pyrazol-5-amine (**2d**) and 1-benzyl-3-phenyl-1*H*-pyrazol-5-amine (**2f**) were similar to the reactions with 1,3-dimethyl-1*H*-pyrazol-5-amine (**2a**) described above; that is, under basic conditions, the major products were 6*H*-pyrazolo[3,4-*c*]isothiazoles **5d** and **5f** (45 and 41%, respectively) (Table 1, entries 4 and 6, conditions A), while under acidic conditions, the major products were *N*-(dithiazolylidene)pyrazolamines **3d** and **3f** (73 and 55%, respectively) (Table 1, entries 4 and 6, condition B). Unexpectedly, under conditions B, 1-benzyl-3-methyl-1*H*-pyrazol-5-amine (**2e**) reacted with Appel salt **1** to give pyrazolo[3,4-*c*]isothiazole **5e** (26%) as a major product and the desired *N*-(dithiazolylidene)pyrazolamine **3e** in only trace amounts. 1-Benzyl-*N*-(dithiazolylidene)pyrazolamine **3e** was formed in somewhat higher yield (17%) when the free base of 1-benzyl-3-methyl-1*H*-pyrazol-5-amine (**2e**) was used (Table 1, entry 5, conditions B). Reaction of Appel salt **1** with 1-(*tert*-butyl)-3-methyl- and 1-(*tert*-butyl)-3-phenyl-1*H*-pyrazol-5-amines **2g** and **2h** using either conditions A or B gave only the 6-(*tert*-butyl)-4-methyl- and 6-(*tert*-butyl)-4-phenyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitriles **5g** and **5h**, respectively, and none of the corresponding 1-(*tert*-butyl)-*N*-(dithiazolylidene)pyrazolamines (Table 1, entry 7 and 8). Presumably, the bulky *tert*-butyl group at N-1 shielded the neighboring C-5 amine, promoting attack at the enaminic C-4 position. For 1-phenyl-1*H*-pyrazol-5-amines **2i** and **2j**, using both sets of reaction conditions, the reaction mixtures were more complex, and the products **3i**, **3j**, **5i**, and **5j** were obtained in low to moderate yields (Table 1, entries 9 and 10).

2.3. Mechanistic Rationale. The formation of *N*-(dithiazolylidene)pyrazolamine **3** was a result of the expected normal attack of the exocyclic primary amine at the highly electrophilic C-5 position of Appel salt **1**. The formation of 6*H*-pyrazolo[3,4-*c*]isothiazole **5**, however, can result from the ambident activity of 1*H*-pyrazol-5-amines **2**, for example, their ability to also react via the C-4 position (enaminic attack) (Scheme 6).

Scheme 6. Proposed Reaction Mechanism for the Formation of 6*H*-Pyrazolo[3,4-*c*]isothiazoles 5



While the proposed ylidene **15** was not observed in the reaction mixture, similar intermediates have been invoked for the reaction of Appel salt **1** with the primary enamines (*E*)-methyl 3-aminobut-2-enoate **6**[19] and 6-amino-1,3-dialkyluracils **7** (Scheme 2).[20] The exocyclic imine of intermediate **15** assisted by the pyrazole N-1 ring nitrogen can cyclize onto the dithiazole S-1 atom, leading to the formation of the isothiazole with concomitant cleavage of the dithiazole that gives *N*-

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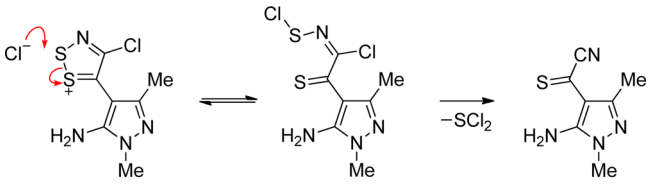
mercaptocarbimidoyl chloride intermediate **16**. From this intermediate, the dithiazole S-2 sulfur atom can extrude as S_8 via a bimolecular sulfur chain extension process,[22] and the isolation of trisulfide **11** tentatively supports this. Interestingly, chloride-mediated thiophilic ring-opening of the proposed dithiazolium intermediate **14** can lead to isomeric sulfenyl chloride **17** that can lose sulfur dichloride to afford carbothioyl cyanide **10** (Scheme 7). The isolation of carbothioyl cyanide **10** adds tentative support for the above mechanistic rationale.

Scheme 7. Possible Route to 5-Amino-1,3-dimethyl-1*H*-pyrazole-4-carbothioyl Cyanide (10)



14 **17** **10**

The structure of disulfide **12** provides further evidence that pyrazolamine **2a** reacted with Appel salt **1** via the enaminic C-4 carbon, a necessary criteria for the formation of pyrazoloisothiazoles **5**. A tentative but plausible mechanism for the formation of disulfide **12** can involve the condensation of three components: the proposed *N*-mercaptocarbimidoyl chloride intermediate **16** could add to carbothioyl cyanide **10** to give a disulfide intermediate that then captures a molecule of Appel salt **1** to give the ketenimine **18**. The thiophilic addition of thiols to thiones to give disulfides is well documented.[23] The highly electrophilic ketenimine **18**, now activated by the dithiazolium cation, can rapidly capture chloride to give the neutral species **12** (Scheme 8).

It is not possible at this stage to predict the order of events leading to the final product; nevertheless, the structures of disulfide **12**, carbothioyl cyanide **10**, and pyrazoloisothiazoles **5** clearly support that, in these cases, Appel salt **1** reacted at the pyrazoles enaminic C-4 carbon. Interestingly, on extending the reaction time, the minor side products **10**–**12** disappeared from the reaction mixture (by TLC), suggesting that they could be possible intermediates to the final products.

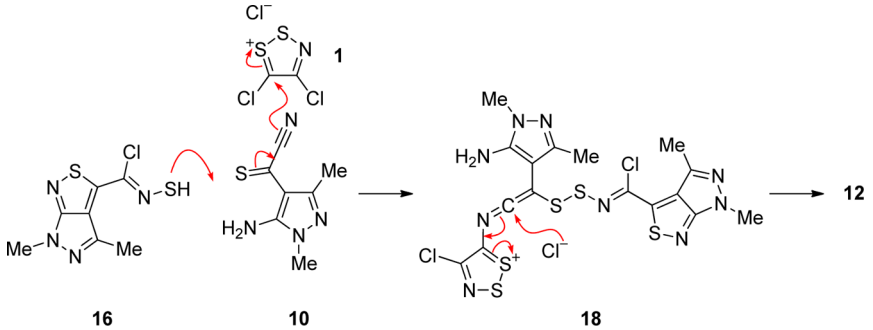
1*H*-Pyrazol-5-amines are widely used in synthesis;[18] however, predicting their selectivity toward electrophiles (i.e., 5-NH_2 vs C-4 attack) is not trivial as many factors can influence the course of the reaction. In our case, where Appel salt **1** is used as the electrophile and 1-alkylpyrazol-5-amines as the nucleophile, the results described above indicate that the determining factor is the pH of the reaction medium. Under basic conditions (conditions A), reaction at the C-4 pyrazole carbon (enaminic attack) was favored, while under acidic conditions (conditions B), the expected direct (normal) attack of the pyrazole exocylic primary amine was observed. This could be explained in terms of the initial protonation of 5-aminopyrazoles that occurs on the ring nitrogens,[21] thus reducing the electron density of the pyrazole ring and deactivating enaminic-like behavior. The results become more complex, however, when the N-1 substituent is changed. In the case of bulky *tert*-butyl groups at N-1 (e.g., pyrazol-5-amines **2g** and **2h**), only the formation of isothiazole is observed in reasonable quantities. The reactions of 1-phenylpyrazolamines **2i** and **2j** were also complex, affording the desired products in only low to moderate yields. Presumably, this was owed to a combination of both steric and electronic effects; the N-1 phenyl group was both considerably more bulky and inductively less electron releasing than the methyl group, simultaneously shielding the 5-amino group and deactivating enaminic C-4 position from reaction with the Appel salt **1**. Lastly, 1-unsubstituted pyrazolamines **2b** and **2c**, regardless the reaction conditions, reacted mainly via the exocyclic amino group, possibly owing to the 1*H*-pyrazol-3-amine prototautomeric form being more favorable than the 1*H*-pyrazol-5-amine form.[24]

2.4. Synthesis of 1*H*-Pyrazolo[3,4-*d*]thiazole-5-carbonitriles 4 via Thermolysis of *N*-(Dithiazolylidene)-pyrazolamines 3. With a series of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1*H*-pyrazol-5-amines **3** in hand, we then investigated their thermal behavior. Using differential scanning calorimetry (DSC), we determined the thermal decomposition points of each compound. Then, neat samples (0.1 mmol) were thermolyzed at temperatures slightly above their decomposition onset points under an argon atmosphere (Table 2).

In general, thermolysis of 1,3-disubstituted *N*-(dithiazolylidene)pyrazolamines **3** gave the desired 1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitriles **4**, in 69–85% yields (Table 2, entries 1 and 4–8). The reactions were accompanied by the formation of elemental sulfur (S_8), traces of unreacted *N*-(dithiazolylidene)pyrazolamines **3**, and, in some cases, minor unidentified side products, which could be avoided by raising the thermolysis temperature. In the case of the 1-unsubstituted analogues *N*-(dithiazolylidene)pyrazolamines **3b** and **3c**, thermolysis gave mainly S_8 and intractable black solids (Table 2, entries 2 and 3).

2.5. Routes to *N*-Unsubstituted Pyrazolo[3,4-*c*]-isothiazole-3-carbonitriles and Pyrazolo[3,4-*d*]thiazole-5-carbonitriles. The above syntheses worked particularly well for 1-alkyl or aryl-substituted 1*H*-pyrazol-5-amines but not for

Scheme 8. Tentative Mechanism for the Formation of Disulfide 12



16 **10** **18**

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Table 2. Thermolysis of *N*-(Dithiazolylidene)pyrazol-5-amines 3

3 4

entry	R^1	R^2	dec onset (°C)	temp (°C)	time (min)	yields 4 (%)
1	Me	Me	158.2	170	15	**4a** (77)
2	H	Me	158.4	170	10	**4b** ([a])
3	H	Ph	196.3	210	10	**4c** ([a])
4	Me	Ph	149.0	170	15	**4d** (83)
5	Bn	Me	142.1	180	15	**4e** (69)
6	Bn	Ph	161.6	200	15	**4f** (85)
7	Ph	Me	126.8	150	15	**4g** (83)
8	Ph	Ph	160.6	180	15	**4h** (78)

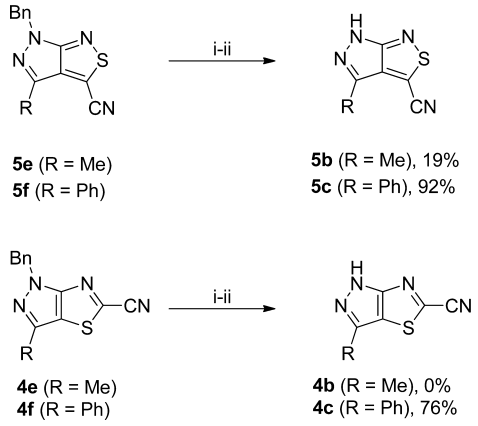
[a]Intractable black solids.

1-unsubstituted pyrazolamines: The reaction of 1-unsubstituted pyrazolamines **2b** and **2c** with Appel salt **1** gave the 6-unsubstituted pyrazolo[3,4-*c*]isothiazole-3-carbonitriles **5b** and **5c** in low yields [Table 1, entries 2 (4%) and 3 (7%), respectively], while the thermolysis of the readily obtained 1-unsubstituted *N*-(dithiazolylidene)pyrazolamines **3b** and **3c** gave mainly S_8 and intractable black solids (Table 2, entries 2 and 3). As such, we proposed alternative syntheses via either protodebenzylation of 6-benzylpyrazolo[3,4-*c*]isothiazoles (**5e** and **5f**) and 1-benzylpyrazolo[3,4-*d*]thiazole-5-carbonitriles (**4e** and **4f**) or protodebutylation of 6-(*tert*-butyl)pyrazolo[3,4-*c*]isothiazoles (**5g** and **5h**).

Initial efforts to debenzylate pyrazolothiazole **4f** or pyrazoloisothiazole **5f** using typical debenzylation methods [Pd/C (5 mol %), H_2 (2 atm); BBr_3 (10 equiv) in DCM;[25] cerium ammonium nitrate (CAN) (6 equiv) in MeCN/H_2O;[26] Na, $NH_3(l)$] failed. Nevertheless, by using dibromine and AIBN[27] followed by an alkali work-up needed to hydrolyze any *N*-benzoylated side products, we were able to obtain both 3-phenyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitrile (**4c**) and 4-phenyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5c**) in good yields (76 and 92%, respectively). Unfortunately, for the methyl analogues **4e** and **5e**, the Br_2/AIBN debenzylation conditions worked less well, affording complex mixtures (by TLC) and only a low yield (19%) of *N*-unsubstituted pyrazoloisothiazole **5b** was obtained from the latter (Scheme 9).

An alternative route to 6-unsubstituted pyrazolo[3,4-*c*]-isothiazoles **5b** and **5c** involved treating the available *N*-benzyl and *N*-(*tert*-butyl) analogues **5e–h** with acid. Initially, the 4-phenyl-6*H*-pyrazolo[3,4-*c*]isothiazoles **5f** and **5h** were treated with neat AcOH (pK_a 4.76)[28] and heated to ca. 118 °C for 3 d, but only the corresponding carboxamides **19a** and **19b** were obtained, both in 83% yield. Fortunately, by using concd H_2SO_4[29] and raising the reaction temperature to ca. 60 °C for 1–5 h, pyrazolo[3,4-*c*]isothiazoles **5e–5h** were fully converted into the corresponding 6*H*-pyrazolo[3,4-*c*]isothiazole-3-carboxamides **20a** and **20b** in 59–98% yields. For 6-(*tert*-butyl)-6*H*-pyrazolo[3,4-*c*]isothiazoles **5g** and **5h**, the debutylation was also effective when the reaction was performed at ca. 20 °C for 1 d. In the case of 6-benzyl-6*H*-pyrazolo[3,4-*c*]isothiazoles **5e** and **5f**, however, the reaction was not very successful, and degradation was observed. Subsequent dehydration of carboxamides **20a** and **20b** with neat $POCl_3$ at ca. 60 °C gave the desired carbonitriles **5b** and **5c**, respectively, in good overall yields (50–90%). Nevertheless, similar treatment of the 1-benzyl-1*H*-pyrazolo[3,4-*d*]thiazoles **4e** and **4f** with neat concd H_2SO_4 at ca. 60 °C led to degradation, while selective hydration of the nitriles could be achieved by carrying out the reaction at ca. 20 °C for 2 h to give carboxamides **21a** (85%) and **21b** (88%) (Scheme 10). Extended reaction times at ca. 20 °C also led to degradation.

Scheme 9[a]



[a]Reagents and conditions: (i) Br_2 (3 equiv), AIBN (0.4 equiv), PhH/H_2O (2:1), ca. 80 °C, 7 h; (ii) NaOH (1 equiv), EtOH, ca. 78 °C, 12 h.

3. CONCLUSIONS

1*H*-Pyrazol-5-amines **2** react with Appel salt **1** either via normal or enaminic attack, depending on the pH of the medium. Basic conditions favor formation of 6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitriles **5** (enaminic attack), while acidic conditions favor the formation of (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1*H*-pyrazol-5-amines **3** (normal attack). Exceptions were 1-(*tert*-butyl)pyrazol-5-amines **2g** and **2h** and 1-unsubstituted pyrazol-5-amines **2b** and **2c**, which, independent of the reaction conditions, gave as major products pyrazoloisothiazoles **5g** and **5h** and dithiazolylidene-1*H*-pyrazol-5-amines **3b** and **3c**, respectively. On thermolysis, (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1*H*-pyrazol-5-amines **3** gave 1*H*-pyrazolo[3,4-*d*]thiazoles **4** in good yields. Furthermore, single crystal X-ray crystallography supported the structure of 4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile **5a**, which was previously mistaken to be 1,3-dimethyl-1*H*-pyrazolo[3,4-*d*]thiazole-3-carbonitrile **4a**.

4. EXPERIMENTAL SECTION

4.1. General Methods and Materials. DCM was freshly distilled from CaH_2 under argon. Reactions were protected from atmospheric moisture by $CaCl_2$ drying tubes. 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 (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 silica gel 60 (less than 0.063 mm).[30] Melting points were determined using a Koefler-Hotstage

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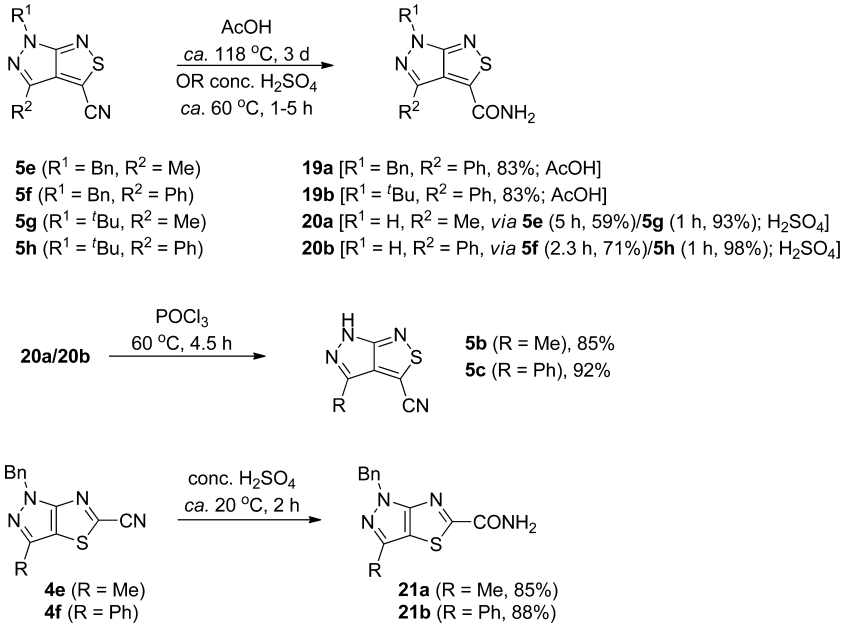
Scheme 10. Preparation of 6-Unsubstituted Pyrazoloisothiazoles 5b and 5c and 1-Benzyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carboxamides 21



microscope apparatus or a DSC with samples hermetically sealed in aluminum pans under an argon atmosphere and using heating rates of 5 °C/min. Solvents used for recrystallization are indicated after the melting point. UV/vis spectra were obtained using a UV/vis spectrophotometer, and inflections are identified by the abbreviation "inf". IR spectra were recorded on an FTIR spectrometer with a Ge ATR accessory; strong, medium, and weak peaks are represented by s, m, and w, respectively. ^{1}H and ^{13}C NMR spectra were recorded at either 300 and 75 MHz, respectively, or at 500 and 125 MHz, respectively. Deuterated solvents were used for homonuclear lock, and the signals are referenced to the deuterated solvent peaks. DEPT or APT NMR studies identified quaternary and tertiary carbons, which are indicated by (s) and (d) notations, respectively. Low resolution (EI) mass spectra were recorded on a GCMS fitted with a direct inlet probe. MALDI-TOF MS were conducted on a time-of-flight (TOF) mass spectrometer. 4,5-Dichloro-1,2,3-dithiazolium chloride (**1**),[12] 1,3-dimethyl-1*H*-pyrazol-5-amine (**2a**),[31] 3-methyl-1*H*-pyrazol-5-amine (**2b**),[32] 3-phenyl-1*H*-pyrazol-5-amine (**2c**),[33] 1-methyl-3-phenyl-1*H*-pyrazol-5-amine (**2d**),[33] 1-benzyl-3-methyl-1*H*-pyrazol-5-amine (**2e**),[34] 1-benzyl-3-phenyl-1*H*-pyrazol-5-amine (**2f**),[35] 1-(*tert*-butyl)-3-methyl-1*H*-pyrazol-5-amine (**2g**),[36] 1-(*tert*-butyl)-3-phenyl-1*H*-pyrazol-5-amine (**2h**),[37] 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2i**),[38] and 1,3-diphenyl-1*H*-pyrazol-5-amine (**2j**)[33] were prepared according to literature procedures.

4.2. Reaction of 1,3-Dimethyl-1*H*-pyrazol-5-amine (2a) with 4,5-Dichloro-1,2,3-dithiazolium Chloride (1). To a stirred suspension of 4,5-dichloro-1,2,3-dithiazolium chloride (**1**) (1.00 g, 4.8 mmol) in DCM (20 mL) at ca. 20 °C under argon atmosphere was added in one portion a solution of 1,3-dimethyl-1*H*-pyrazol-5-amine (**2a**) (0.53 g, 4.8 mmol) and lutidine (1.12 mL, 9.6 mmol) in DCM (20 mL). The mixture was stirred for 1 h and then adsorbed on silica and chromatographed (DCM) to give 4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5a**) (99 mg, 12%) as colorless needles; mp 102−106 °C (from *c*-hexane); R_f 0.45 (DCM). Found: C, 47.31; H, 3.38; N, 31.30. $C_7H_6N_4S$ requires: C, 47.18; H, 3.39; N, 31.44%. λ_{max} (DCM) 291 (log ε 2.73), 369 (2.39); ν_{max}/cm^{-1} 2992w, 2928w, and 2851w (CH_3); 2218s (C≡N); 1582s, 1514m, 1441m, 1410m, 1383m, 1331m, 1246m, 1229m, 1034m, 986m, 934w, 899s, 841m, 745m; δ_H (500 MHz; $CDCl_3$) 3.90 (3H, s), 2.53 (3H, s); δ_C (125 MHz; $CDCl_3$) 165.7 (s), 135.4 (s), 130.3 (s), 120.4 (s), 110.3 (s), 34.8 (q), 13.1 (q); *m*/*z* (EI) 178 (M^+, 100%), 163 (22), 150 (7), 135 (5), 123 (5), 108 (9), 91 (10), 70 (24), 64 (7), 46 (8), 43 (41). Further elution (DCM/*t*-BuOMe, 98:2) gave (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1,3-dimethyl-1*H*-pyrazol-5-amine (**3a**) (58 mg, 5%) as yellow prisms; mp (DSC) onset, 146.3 °C; peak max, 156.6 °C; dec onset, 158.2 °C; peak max, 158.9 °C (from *c*-hexane/DCE); R_f 0.67 (DCM/*t*-BuOMe, 9:1). Found: C, 34.13; H, 2.76; N, 22.81. $C_7H_7ClN_4S_2$ requires: C, 34.07; H, 2.86; N, 22.71%). λ_{max} (DCM) 250 (log ε 2.83), 270 (2.58), 382 inf (2.86), 389 inf (2.85), 401 (2.91), 418 inf (2.79); ν_{max}/cm^{-1} 2932w (CH_3); 1578s, 1555w, 1514m, 1443m, 1410w, 1373w, 1360w, 1292m, 1192m, 1148m, 1049w, 1013m, 878s, 856m, 777s; δ_H (500 MHz; $CDCl_3$) 6.23 (1H, s), 3.90 (3H, s), 2.34 (3H, s); δ_C (125 MHz; $CDCl_3$) 153.9 (s), 149.0 (s), 147.6 (s), 145.9 (s), 94.5 (d), 34.9 (q), 14.2 (q); *m*/*z* (EI) 248 (M^+ + 2, 40%), 246 (M^+, 92), 211 (M^+−Cl, 73), 182 (6), 179 (22), 170 (8), 152 (31), 147 (20), 137 (8), 127 (14), 125 (18), 120 (100), 110 (8), 106 (20), 102 (31), 95 (20), 93 (23), 80 (21), 70 (46), 64 (64), 52 (25), 42 (38). Further elution (DCM/*t*-BuOMe, 98:2) gave 5-amino-1,3-dimethyl-1*H*-pyrazole-4-carbothioyl cyanide (**10**) (33.5 mg, 4%) as orange plates; mp 212−213 °C (from $CHCl_3$); R_f 0.23 (DCM/*t*-BuOMe, 9:1). Found: C, 46.53; H, 4.33; N, 30.95. $C_7H_8N_4S$ requires: C, 46.65; H, 4.47; N, 31.09%. λ_{max} (DCM) 253 (log ε 3.76), 367 (4.06), 414 (4.11); ν_{max}/cm^{-1} 3339m (NH_2), 3211w, 3165w, 3011w, 2988w, 2965w, and 2930w (CH_3); 2226w (C≡N), 1632s, 1562m, 1557m, 1526m, 1493s, 1452m, 1435m, 1389m, 1339m, 1238w, 1215w, 1128w, 1024m, 989m, 972m, 955m, 862w, 739w; δ_H (500 MHz; $CDCl_3$) 7.23 (2H, br s), 3.59 (3H, s), 2.57 (3H, s); δ_C (125 MHz; DMSO-d_6) 165.2 (s), 154.0 (s), 145.7 (s), 122.6 (s), 116.2 (s), 33.9 (q), 14.0 (q); MALDI-TOF MS (*m*/*z*) 181 (MH^+ + 1, 39%), 181 (MH^+, 100), 154 (79), 111 (29). Further elution (DCM/*t*-BuOMe, 95:5) gave (3*Z*,3′*Z*)-*N*′,*N*″-3-trisulfanediylbis(4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]-isothiazole-3-carbimidoyl chloride) (**11**) (125 mg, 12%) as yellow needles; mp (DSC) onset, 178.7 °C; peak max, 184.0 °C; dec onset, 191.4 °C; peak max, 198.6 °C (from DCE); R_f 0.67 (DCM/*t*-BuOMe, 8:2). Found: C, 32.22; H, 2.11; N, 21.50. $C_{14}H_{12}Cl_2N_8S_5$ requires: C, 32.12; H, 2.31; N, 21.40%. λ_{max} (DCM) 310 (log ε 3.60), 408 (3.60); ν_{max}/cm^{-1} 2990w, 2959w, and 2913w (CH_3); 1578m, 1557m, 1510m, 1454m, 1435m, 1406m, 1377m, 1335m, 1244m, 1219m, 1190m, 1040m, 989m, 966m, 935w, 845m, 800s; δ_H (500 MHz; CD_2Cl_2) 3.81 (3H, s), 2.56 (3H, s); δ_C (125 MHz; CD_2Cl_2) 167.3 (s), 150.9 (s), 137.1 (s), 132.3 (s), 124.9 (s), 34.6 (q), 15.9 (q); MALDI-TOF MS (*m*/*z*): 525 (M^+ + 3, 27%), 523 (M^+ + 1, 78), 521 (M^+ − 1, 65), 485 (12), 460 (7), 458 (9), 425 (15), 389 (4), 309 (14), 307 (23), 276 (12), 249 (56), 247 (100), 244 (74), 227 (9), 213 (40). Further

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elution (DCM/*t*-BuOMe, 6:4) gave (*Z*)-*N*-{[(*Z*)-1-(5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)-2-chloro-2-[(*Z*)-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino]vinyl]disulfanyl}-4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbimidoyl chloride (**12**) (154 mg, 13%) as red needles; mp 143−145 °C (from *n*-pentane/DCM); R_f 0.27 (DCM/*t*-BuOMe, 4:6). Found: C, 32.13; H, 2.21; N, 20.94. $C_{16}H_{14}Cl_3N_9S_5$ requires: C, 32.12; H, 2.31; N, 21.04%. λ_{max}(DCM) 313 (log ε 4.18), 417 (4.28), 465 inf (4.16); ν_{max}/cm^{-1} 3327w and 3196w (NH_2), 2934w (CH_3), 1649m, 1557s, 1512m, 1485m, 1423m, 1404m, 1383m, 1339m, 1298m, 1227m, 1161s, 1107w, 1043w, 993w, 968m, 897w, 859s, 845m, 799s, 785s, 735m; δ_H(500 MHz; $CDCl_3$) 3.83 (3H, s), 3.77 (2H, br s), 3.57 (3H, s), 2.58 (3H, s), 2.03 (3H, s); δ_C(125 MHz; $CDCl_3$) 166.7 (s), 152.8 (s), 151.1 (s), 149.3 (s), 147.2 (s), 143.6 (s), 136.9 (s), 130.0 (s), 129.3 (s), 128.9 (s), 124.2 (s), 99.3 (s), 34.3 (q), 34.2 (q), 15.7 (q), 13.7 (q); MALDI-TOF MS (*m*/*z*): 603 (M^+ + 6, 18%), 601 (M^+ + 4, 51), 599 (M^+ + 2, 96), 597 (M^+, 100), 530 (19), 499 (14), 385 (32), 383 (33), 351 (19), 349 (34), 347 (67), 285 (28), 283 (97), 247 (12), 212 (9), 176 (6).

4.3. Thermolysis of Side Products 11 and 12 (Scheme 4). *4.3.1. Thermolysis of Trisulfide **11** (Typical Procedure).* A stirred neat sample of (3*Z*,3′*Z*)-*N*′,*N*″-trisulfanediylbis(4,6-dimethyl-6*H*-pyrazolo-[3,4-*c*]isothiazole-3-carbimidoyl chloride) (**11**) (20.0 mg, 0.04 mmol) under an argon atmosphere was immersed into a preheated Wood's metal bath at ca. 250 °C. After 4 min, the mixture was allowed to cool to ca. 20 °C and extracted with DCM (3 × 1 mL). The combined extracts were adsorbed onto silica and chromatographed (*n*-hexane) to give S_8. Further elution (DCM/*t*-BuOMe, 99:1) gave 4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5a**) (12.1 mg, 89%) as colorless needles; mp 102−106 °C (from *c*-hexane); R_f 0.45 (DCM); identical to that described above.

*4.3.2. Thermolysis of Disulfide **12**.* Similar treatment of (*Z*)-*N*-{[(*Z*)-1-(5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)-2-chloro-2-[(*Z*)-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino]vinyl]disulfanyl}-4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbimidoyl chloride (**12**) (20.0 mg, 0.03 mmol) at ca. 200 °C for 2 min gave 4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5a**) (5.8 mg, 49%) as colorless needles; mp 102−106 °C (from *c*-hexane); R_f 0.45 (DCM); identical to that described above.

4.4. Reaction of Trisulfide 11 and Disulfide 12 with Concentrated H_2SO_4 (Scheme 4). To concd H_2SO_4 (1 mL) at ca. 20 °C was added either (3*Z*,3′*Z*)-*N*′,*N*″-trisulfanediylbis(4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbimidoyl chloride) (**11**) (20.0 mg, 0.04 mmol) or (*Z*)-*N*-{[(*Z*)-1-(5-amino-1,3-dimethyl-1*H*-pyrazol-4-yl)-2-chloro-2-[(*Z*)-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-amino]vinyl]disulfanyl}-4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbimidoyl chloride (**12**) (20.0 mg, 0.03 mmol). On consumption of either compound **11** or **12** (by TLC), the reaction mixture was poured onto crushed ice, left to warm to ca. 20 °C, neutralized (sat. $NaHCO_3$) and extracted with *t*-BuOMe (4 × 10 mL). The combined extracts were then dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was dissolved in THF (5 mL), adsorbed onto silica, and chromatographed (*t*-BuOMe) to give 4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carboxamide (**13**) (14.8 mg, 99% from **11** and 4.0 mg, 34% from **12**) as colorless needles; mp 181−182 °C (from *c*-hexane/EtOH); R_f 0.33 (*t*-BuOMe). Found: C, 42.79; H, 4.13; N, 28.40. $C_7H_8N_4OS$ requires: C, 42.85; H, 4.11; N, 28.55%). λ_{max} (EtOH) 224 (log ε 2.87), 282 (2.94), 351 (2.64); ν_{max}/cm^{-1} 3356m and 3163m (NH_2), 1692s (C═O), 1626m, 1589m, 1516m, 1443m, 1389s, 1377s, 1317m, 1215m, 1123m, 1032m, 989w, 934m, 920w, 827m, 781m; δ_H (300 MHz; DMSO-d_6) 8.09 (1H, br s), 7.96 (1H, br s), 3.75 (3H, s), 2.44 (3H, s); δ_C (75 MHz; DMSO-d_6) 166.0 (s), 160.3 (s), 150.9 (s), 135.8 (s), 126.1 (s), 34.1 (q), 14.2 (q); *m*/*z* (EI) 196 (M^+, 100%), 180 (21), 151 (33), 138 (3), 125 (4), 108 (10), 98 (4), 94 (4), 90 (7), 82 (13), 69 (8), 64 (7).

4.5. Dehydration of 4,6-Dimethyl-6*H*-pyrazolo[3,4-*c*]-isothiazole-3-carboxamide (13). To a stirred solution of 4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carboxamide (**13**) (19.6 mg, 0.1 mmol) in toluene (1 mL) was added in one portion $POCl_3$ (100 μL, 1 mmol). The reaction mixture was then heated to ca. 110 °C for 3 h. The mixture was then left to cool to ca. 20 °C, absorbed onto silica, and chromatographed (DCM/*t*-BuOMe, 99:1) to give 4,6-dimethyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5a**) (17.5 mg, 98%) as colorless needles; mp 102−106 °C (from *c*-hexane); R_f 0.45 (DCM); identical to that described above.

4.6. Reaction of 1*H*-Pyrazol-5-amines 2 with 4,5-Dichloro-1,2,3-dithiazolium Chloride (1). See Table 1 for yields.

General Procedure A: To a stirred solution of the appropriate 1*H*-pyrazol-5-amine **2** (0.48 mmol) in DCM (4 mL) at ca. 20 °C and protected with $CaCl_2$ drying tube was added in one portion lutidine (112 μL, 0.96 mmol). The reaction mixture was then stirred for 5 min, and then Appel salt **1** (100 mg, 0.48 mmol) was added. After an additional 15 h of stirring at ca. 20 °C, the reaction mixture was adsorbed onto silica and chromatographed.

General Procedure B: A stirred solution of the appropriate 1*H*-pyrazol-5-amine **2** (0.48 mmol) in dry DCM (4 mL) at ca. 20 °C was purged for 30 s with HCl (g). After the purge was complete, to the reaction mixture was added in one portion Appel salt **1** (100 mg, 0.48 mmol). The reaction mixture was then stirred for 12 h, and lutidine (112 μL, 0.96 mmol) was added in one portion. The reaction mixture was stirred for an additional 3 h, adsorbed onto silica, and chromatographed.

*4.6.1. (Z)-N-(4-Chloro-5H-1,2,3-dithiazol-5-ylidene)-3-methyl-1H-pyrazol-5-amine (**3b**).* Procedure A: 72.5 mg, 65%. Procedure B: 83 mg, 74%. Chromatography eluent: DCM/*t*-BuOMe, 95:5. Orange prisms; mp (DSC) onset, 150.8 °C; peak max, 154.8 °C; dec onset, 158.4 °C; peak max, 161.1 °C (from *c*-hexane/DCE); R_f 0.48 (DCM/*t*-BuOMe, 98:2). Found: C, 31.06; H, 2.19; N, 23.92. $C_6H_5ClN_4S_2$ requires: C, 30.97; H, 2.17; N, 24.08%. λ_{max} (DCM) 250 (log ε 3.98), 255 inf (3.93), 274 inf (3.41), 375 inf (3.93), 389 (4.02), 406 inf (3.90); ν_{max}/cm^{-1} 3208m (NH), 3150w, 2928w and 2862w (CH_3), 1578m, 1543s, 1533m, 1491m, 1449w, 1396m, 1375m, 1281m, 1175m, 1136m, 1026w, 1003m, 876s, 868s, 826w, 779m, 768s; δ_H (500 MHz; DMSO-d_6) 12.93 (1H, s), 6.24 (1H, s), 2.30 (3H, s); δ_C (125 MHz; DMSO-d_6) 154.5 (s), 154.2 (s), 148.2 (s), 141.5 (s), 101.4 (d), 11.4 (q); MALDI-TOF MS (*m*/*z*) 235 (MH^+ + 2, 56%), 233 (MH^+, 100), 197 (91), 140 (67).

*4.6.2. (Z)-N-(4-Chloro-5H-1,2,3-dithiazol-5-ylidene)-3-phenyl-1H-pyrazol-5-amine (**3c**).* Procedure A: 82 mg, 58%. Procedure B: 130 mg, 92%. Chromatography eluent: DCM. Orange needles; mp (DSC) onset, 190.9 °C; peak max, 193.8 °C; dec onset, 196.3 °C; peak max, 199.9 °C (from *c*-hexane/DCE); R_f 0.44 (DCM). Found: C, 44.80; H, 2.32; N, 18.94. $C_{11}H_7ClN_4S_2$ requires: C, 44.82; H, 2.39; N, 19.01%. λ_{max} (DCM) 258 (log ε 4.50), 378 inf (4.05), 391 (4.14), 408 inf (4.00); ν_{max}/cm^{-1} 3341m (NH), 3154w, 3065w, and 3017w (Ar CH), 1549m, 1522w, 1501w, 1487m, 1472m, 1456m, 1396w, 1314w, 1296w, 1273w, 1204m, 1159m, 1009m, 957w, 914w, 868m, 816w, 795w, 727s; δ_H (500 MHz; DMSO-d_6) 13.72 (1H, s), 7.83 (2H, d, *J* 7.5), 7.50 (2H, dd, *J* 7.8, 7.8), 7.40 (1H, dd, *J* 7.3, 7.3), 6.98 (1H, d, *J* 2.0); δ_C(125 MHz; DMSO-d_6) 154.8 (s), 154.3 (s), 147.6 (s), 144.2 (s), 129.0 (d), 128.8 (s), 128.6 (d), 125.2 (d), 99.4 (d); MALDI-TOF MS (*m*/*z*) 297 (MH^+ + 2, 28%), 295 (MH^+, 100), 205 (13).

*4.6.3. (Z)-N-(4-Chloro-5H-1,2,3-dithiazol-5-ylidene)-1-methyl-3-phenyl-1H-pyrazol-5-amine (**3d**).* Procedure A: 0%. Procedure B: 108 mg, 73%. Chromatography eluent: *n*-hexane/DCM, 40:60. Yellow needles; mp (DSC) onset, 140.0 °C; peak max, 140.6 °C; dec onset, 149.0 °C; peak max, 150.6 °C (from *c*-hexane); R_f 0.52 (*n*-hexane/DCM, 30:70). Found: C, 46.71; H, 3.01; N, 18.20. $C_{12}H_9ClN_4S_2$ requires: C, 46.67; H, 2.94; N, 18.14%. λ_{max} (DCM) 251 (log ε 4.36), 300 inf (3.59), 376 inf (3.92), 392 inf (4.03), 409 (4.09), 428 inf (3.94); ν_{max}/cm^{-1} 3065w (Ar CH), 2930w and 2847w (CH_3), 1585m, 1547w, 1531w, 1512w, 1491m, 1460m, 1427w, 1352w, 1300m, 1188m, 1144m, 1107w, 1072w, 1034w, 955m, 918w, 870m, 845m, 773s, 748s; δ_H (500 MHz; $CDCl_3$) 7.83 (2H, d, *J* 7.0), 7.43 (2H, dd, *J* 7.8, 7.8), 7.34 (1H, dd, *J* 7.3, 7.3), 6.73 (1H, s), 4.03 (3H, s); δ_C (125 MHz; $CDCl_3$) 154.5 (s), 150.2 (s), 149.0 (s), 146.5 (s), 133.1 (s), 128.7 (d), 128.0 (d), 125.4 (d), 91.8 (d), 35.4 (q); MALDI-TOF MS (*m*/*z*) 311 (MH^+ + 2, 53%), 309 (MH^+, 100), 289 (57), 205 (90).

*4.6.4. (Z)-1-Benzyl-N-(4-chloro-5H-1,2,3-dithiazol-5-ylidene)-3-methyl-1H-pyrazol-5-amine (**3e**).* Procedure A: 0%. Procedure B: 26.5 mg, 17%. Chromatography eluent: DCM. Yellow plates; mp

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(DSC) onset, 138.0 °C; peak max, 140.8 °C; dec onset, 142.1 °C; peak max, 142.6 °C (from *c*-hexane); R_f 0.26 (DCM). Found: C, 48.32; H, 3.52; N, 17.23. $C_{13}H_{11}ClN_4S_2$ requires: C, 48.36; H, 3.43; N, 17.35%). λ_{max} (DCM) 252 (log ε 4.04), 303 (3.58), 388 inf (4.17), 405 (4.23), 425 inf (4.09); ν_{max}/cm^{-1} 3061w, 3042w, 2940w, 1560m, 1551m, 1518m, 1495m, 1456w, 1447w, 1437m, 1369m, 1346w, 1331w, 1306w, 1288w, 1209m, 1204w, 1177w, 1152m, 1121w, 1032w, 1016m, 1001w, 935w, 926w, 880m, 849m, 820m, 791m, 762s, 741m; δ_H (500 MHz; acetone-d_6) 7.37 (2H, d, *J* 7.0), 7.30 (2H, dd, *J* 7.3, 7.3), 7.24 (1H, dd, *J* 7.3, 7.3), 6.35 (1H, s), 5.44 (2H, s), 2.26 (3H, s); δ_C (125 MHz; $CDCl_3$) 154.0 (s), 149.1 (s), 148.1 (s), 145.5 (s), 137.3 (s), 94.9 (d), 51.8 (t), 14.4 (q); MALDI-TOF MS (*m*/*z*) 325 (MH^++2, 56%), 323 (MH^+, 100), 91 (59).

*4.6.5. (Z)-1-Benzyl-N-(4-chloro-5H-1,2,3-dithiazol-5-ylidene)-3-phenyl-1H-pyrazol-5-amine (**3f**).* Procedure A: 0%. Procedure B: 101.5 mg, 55%. Chromatography eluent: *n*-hexane/DCM, 60:40. Yellow needles; mp (DSC) onset, 158.9 °C; peak max, 160.0 °C; dec onset, 161.6 °C; peak max, 172.9 °C (from *c*-hexane); R_f 0.30 (*n*-hexane/DCM, 50:50) Found: C, 56.12; H, 3.50; N, 14.67. $C_{18}H_{13}ClN_4S_2$ requires: C, 56.17; H, 3.40; N, 14.56%. λ_{max}(DCM) 258 (log ε 4.44), 394 inf (4.09), 411 (4.14), 434 inf (3.98); ν_{max}/cm^{-1} 3065w and 3024w (Ar CH), 2947w (CH_3), 1564m, 1549m, 1526w, 1501m, 1493m, 1487m, 1462m, 1454m, 1441m, 1423w, 1354w, 1327w, 1308m, 1292w, 1206m, 1200m, 1177w, 1163m, 1155m, 1136m, 1088m, 1072w, 1028w, 970w, 955m, 922w, 910m, 878m, 849m, 837w, 822w, 791m, 777m, 762s; δ_H (500 MHz; DMSO-d_6) 7.86 (2H, d, *J* 7.0), 7.42 (2H, dd, *J* 7.5, 7.5), 7.34−7.25 (6H, m), 6.90 (1H, s), 5.49 (2H, s); δ_C (125 MHz; DMSO-d_6) 157.1 (s), 149.6 (s), 147.7 (s), 146.6 (s), 137.4 (s), 132.8 (s), 128.8 (d), 128.6 (d), 128.1 (d), 127.9 (d), 127.7 (d), 125.2 (d), 91.9 (d), 51.3 (t); MALDI-TOF MS (*m*/*z*) 387 (MH^++2, 29%), 385 (MH^+, 76%), 90 (100).

*4.6.6. (Z)-N-(4-Chloro-5H-1,2,3-dithiazol-5-ylidene)-3-methyl-1-phenyl-1H-pyrazol-5-amine (**3i**).* Procedure A: 0%. Procedure B: 32.5 mg, 22%). Chromatography eluent: *n*-hexane/DCM, 80:20. Yellow needles; mp (DSC) onset, 121.8 °C; peak max, 122.7 °C; dec onset, 126.8 °C; peak max, 129.2 °C (from *c*-hexane); R_f 0.48 (*n*-hexane/DCM, 30:70). Found: C, 46.58; H, 2.86; N, 18.24. $C_{12}H_9ClN_4S_2$ requires: C, 46.67; H, 2.94; N, 18.14%. λ_{max} (DCM) 243 (log ε 4.27), 263 (4.22), 280 inf (4.09), 397 inf (4.08), 412 (4.11), 432 inf (3.97); ν_{max}/cm^{-1} 3127w (Ar CH), 2928w (CH_3), 1578m, 1520m, 1497m, 1462m, 1431m, 1418m, 1371m, 1317w, 1269w, 1179m, 1148m, 1074m, 1026m, 1011w, 1001w, 982w, 905m, 870m, 837m, 773s, 746m; δ_H (500 MHz; $CDCl_3$) 7.85 (2H, d, *J* 8.0), 7.44 (2H, dd, *J* 7.8, 7.8), 7.31 (1H, dd, *J* 7.5, 7.5), 6.44 (1H, s), 2.44 (3H, s); δ_C (125 MHz; $CDCl_3$) 154.8 (s), 149.3 (s), 149.2 (s), 146.0 (s), 139.2 (s), 128.5 (d), 126.7 (d), 124.0 (d), 96.1 (d), 14.4 (q); MALDI-TOF MS (*m*/*z*) 311 (MH^++2, 94%), 309 (MH^+, 100), 275 (42), 273 (57), 216 (94), 209 (100).

*4.6.7. (Z)-N-(4-Chloro-5H-1,2,3-dithiazol-5-ylidene)-1,3-diphenyl-1H-pyrazol-5-amine (**3j**).* Procedure A: 0%. Procedure B: 16 mg, 9%. Chromatography eluent: *n*-hexane/DCM, 90:10. Yellow needles; mp 92−94 °C (from *c*-hexane); R_f 0.39 (*n*-hexane/DCM, 50:50). Found: C, 55.20; H, 2.86; N, 14.98. $C_{17}H_{11}ClN_4S_2$ requires: C, 55.05; H, 2.99; N, 15.11%. λ_{max} (DCM) 256 (log ε 3.48), 271 inf (3.39), 395 (3.05), 413 (3.06), 431 inf (2.92); ν_{max}/cm^{-1} 3071w (Ar CH), 1578m, 1531m, 1497s, 1456m, 1410w, 1368w, 1304w, 1261w, 1209w, 1186w, 1146m, 1088w, 1074w, 1026w, 1016w, 950m, 916w, 868s, 845w, 829w, 770s, 760m, 745m; δ_H (500 MHz; $CDCl_3$) 7.97 (2H, dd, *J* 8.5, 1.0), 7.94 (2H, dd, *J* 8.5, 1.0), 7.49 (2H, dd, *J* 8.0, 8.0), 7.46 (2H, dd, *J* 7.5, 7.5), 7.39−7.34 (2H, m), 6.92 (1H, s); δ_C (125 MHz; $CDCl_3$) 155.3 (s), 151.3 (s), 149.3 (s), 146.7 (s), 139.2 (s), 132.8 (s), 128.7 (d), 128.6 (d), 128.4 (d), 127.0 (d), 125.7 (d), 124.2 (d), 93.2 (d); MALDI-TOF MS (*m*/*z*) 373 (MH^+ + 2, 49%), 371 (MH^+, 75), 335 (14), 278 (100), 271 (19).

*4.6.8. 4-Methyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5b**).* Procedure A: 3 mg, 4%. Procedure B: 0%. Chromatography eluent: DCM/*t*-BuOMe, 90:10. Colorless needles; mp 182−183.5 °C (from *c*-hexane/$CHCl_3$); R_f 0.33 (DCM/*t*-BuOMe, 97:3). Found: C, 43.79; H, 2.37; N, 34.21. $C_6H_4N_4S$ requires: C, 43.89; H, 2.46; N, 34.12%. λ_{max} (EtOH) 235 (log ε 3.79), 291 (4.61), 351 (3.83); ν_{max}/cm^{-1} 3292s (NH), 2245m and 2226m (C≡N), 1585s, 1506m, 1477w, 1439m, 1383m, 1368m, 1302m, 1215w, 1159w, 1082s, 986m, 897s, 841m, 791s; δ_H (500 MHz; DMSO-d_6) NH resonance missing 2.44 (3H, s); δ_C (125 MHz; DMSO-d_6) 166.5 (s), 135.8 (s), 130.4 (s), 119.2 (s), 111.0 (s), 12.8 (q); MALDI-TOF MS (*m*/*z*) 165 (MH^+, 100%).

*4.6.9. 4-Phenyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5c**).* Procedure A: 7.5 mg, 7%; Procedure B: 0%. Chromatography eluent: DCM/*t*-BuOMe, 90:10. Pale yellow needles; mp 196−197 °C (from *c*-hexane/$CHCl_3$); R_f 0.68 (DCM/*t*-BuOMe, 96:4). Found: C, 58.53; H, 2.56; N, 24.67. $C_{11}H_6N_4S$ requires: C, 58.39; H, 2.67; N, 24.76%. λ_{max} (DCM) 258 (log ε 4.09), 295 (4.11), 368 (3.75); ν_{max}/cm^{-1} 3226m (NH), 3051w (Ar CH), 2224m (C≡N), 1584m, 1512m, 1464m, 1437w, 1385m, 1327m, 1317m, 1298m, 1281m, 1190w, 1101w, 1084m, 1070w, 1013w, 916w, 891s, 856m, 835w, 791s, 777s, 745s; δ_H (500 MHz; $CDCl_3$) 10.04 (1H, s), 8.04 (2H, dd, *J* 8.5, 1.5), 7.55 (2H, dd, *J* 7.5, 7.5), 7.47 (1H, dd, *J* 7.5, 7.5); δ_C (125 MHz; $CDCl_3$) 166.5 (s), 140.9 (s), 130.7 (s), 129.6 (d), 129.2 (d), 127.6 (s), 126.9 (d), 121.9 (s), 111.0 (s); MALDI-TOF MS (*m*/*z*) 229 (MH^+ + 1, 34%), 227 (MH^+, 100), 202 (16), 77 (18).

*4.6.10. 6-Methyl-4-phenyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5d**).* Procedure A: 52 mg, 45%. Procedure B: 6 mg, 5%. Chromatography eluent: *n*-hexane/DCM, 60:40. Yellow needles; mp (DSC) onset, 155.9 °C; peak max, 156.5 °C (from *c*-hexane); R_f 0.54 (*n*-hexane/DCM, 40:60). Found: C, 59.85; H, 3.32; N, 23.23. $C_{12}H_8N_4S$ requires: C, 59.98; H, 3.36; N, 23.32%. λ_{max} (DCM) 265 (log ε 3.34), 291 (3.30), 391 (2.83); ν_{max}/cm^{-1} 3061w (Ar CH), 2941w (CH_3), 2216w (C≡N), 1574m, 1518m, 1491m, 1456m, 1435m, 1406w, 1346m, 1319w, 1298w, 1287m, 1260m, 1231m, 1182w, 1171w, 1157m, 1074w, 1034m, 1024m, 920w, 907w, 881m, 841m, 772m, 739s; δ_H (500 MHz; $CDCl_3$) 8.00 (2H, dd, *J* 8.5, 1.5), 7.52 (2H, dd, *J* 7.5, 7.5), 7.43 (1H, dd, *J* 7.4, 7.4), 4.05 (3H, s); δ_C (125 MHz; $CDCl_3$) 166.2 (s), 138.0 (s), 130.9 (s), 129.2 (d), 129.1 (d), 127.2 (s), 126.6 (d), 121.6 (s), 111.3 (s), 35.2 (q); MALDI-TOF MS (*m*/*z*) 241 (MH^+, 60%), 240 (M^+, 100), 229 (14).

*4.6.11. 6-Benzyl-4-methyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5e**).* Procedure A: 57.5 mg, 47%. Procedure B: 35.5 mg, 29%. Chromatography eluent: DCM. Beige needles; mp 101.5−102 °C (from *n*-hexane at ca. 20 °C); R_f 0.47 (DCM). Found: C, 61.37; H, 3.87; N, 21.93. $C_{13}H_{10}N_4S$ requires: C, 61.40; H, 3.96; N, 22.03%. λ_{max} (DCM) 295 (log ε 4.00), 371 (3.68); ν_{max}/cm^{-1} 3030w (Ar CH), 2976w and 2938w (CH_2 and CH_3), 2220m (C≡N), 1582s, 1510m, 1495m, 1472w, 1454m, 1443m, 1416m, 1387m, 1346m, 1333m, 1298m, 1267s, 1234m, 1204m, 1157w, 1111m, 1107m, 1098m, 1069m, 1069m, 1026w, 903s, 833s, 818m, 770m, 745m; δ_H (500 MHz; $CDCl_3$) 7.36−7.27 (5H, m), 5.37 (2H, s), 2.53 (3H, s); δ_C (125 MHz; $CDCl_3$) 165.3 (s), 136.0 (s), 135.9 (s), 130.7 (s), 128.8 (d), 128.2 (d), 128.0 (d), 120.5 (s), 110.3 (s), 52.3 (t), 13.2 (q); MALDI-TOF MS (*m*/*z*) 255 (MH^+, 100%), 106 (49), 91 (87).

*4.6.12. 6-Benzyl-4-phenyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5f**).* Procedure A: 62.5 mg, 41%. Procedure B: 13.5 mg, 9%. Chromatography eluent: *n*-hexane/DCM, 70:30. Yellow needles, mp (DSC) 109−110.5 °C (from *n*-pentane at ca. −20 °C); R_f 0.36 (*n*-hexane/DCM, 60:40). Found: C, 68.28; H, 3.71; N, 17.64. $C_{18}H_{12}N_4S$ requires: C, 68.33; H, 3.82; N, 17.71%. λ_{max} (DCM) 266 (log ε 4.21), 289 (4.09), 392 (3.81); ν_{max}/cm^{-1} 3065w and 3030w (Ar CH), 2976w and 2941w (CH_2), 2220m (C≡N), 1568m, 1516m, 1497w, 1483m, 1458m, 1435m, 1416m, 1352w, 1342m, 1300w, 1263s, 1244w, 1206w, 1163m, 1117m, 1074m, 1047w, 1024w, 1003w, 974w, 939w, 914m, 878m, 839m, 820m, 777m, 772m, 741s; δ_H (500 MHz; $CDCl_3$) 8.03 (2H, dd, *J* 8.5, 1.5), 7.52 (2H, dd, *J* 7.8, 7.8), 7.45−7.41 (3H, m), 7.36−7.29 (3H, m), 5.52 (2H, d); δ_C(125 MHz; $CDCl_3$) 165.8 (s), 138.5 (s), 135.6 (s), 130.9 (s), 129.3 (d), 129.1 (d), 128.8 (d), 128.3 (d), 128.1 (d), 127.6 (s), 126.8 (d), 121.6 (s), 111.2 (s), 52.7 (t); MALDI-TOF MS (*m*/*z*) 317 (MH^+, 70%), 316 (M^+, 100), 315 (87), 90 (65).

*4.6.13. 6-(tert-Butyl)-4-methyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5g**).* Procedure A: 41 mg, 39%. Procedure B: 22 mg, 21%. Chromatography eluent: *n*-hexane/DCM, 60:40. Colorless needles; mp 63−64 °C (from *n*-pentane at ca. −20 °C); R_f 0.38 (*n*-

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hexane/DCM, 50:50). Found: C, 54.42; H, 5.55; N, 25.34. $C_{10}H_{12}N_4S$ requires: C, 54.52; H, 5.49; N, 25.43%. λ_{max} (DCM) 238 (log ε 3.89), 293 (4.09), 375 (3.75); ν_{max}/cm^{-1} 2982m, 2940w and 2876w (CH_3), 2222m (C≡N), 1574m, 1493m, 1470m, 1456m, 1435w, 1412m, 1398s, 1373m, 1366m, 1329m, 1269m, 1240s, 1167m, 1123s, 1032m, 1001w, 939w, 905s, 843m, 802m, 746m; δ_H(500 MHz; $CDCl_3$) 2.52 (3H, s), 1.69 (9H, s); δ_C(125 MHz; $CDCl_3$) 164.9 (s), 134.1 (s), 131.8 (s), 118.8 (s), 110.6 (s), 59.5 (s), 28.8 (q), 13.1 (q); MALDI-TOF MS (*m*/*z*) 220 (M^+, 100%), 218 (35), 204 (15), 175 (8), 164 (9), 149 (8), 72 (46).

*4.6.14. 6-(tert-Butyl)-4-phenyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5h**).* Procedure A: 51.5 mg, 38%. Procedure B: 50 mg, 37%. Chromatography eluent: *n*-hexane/DCM, 70:30. Yellow needles; mp 120−121.5 °C (from *n*-pentane at ca. −20 °C); R_f 0.64 (*n*-hexane/DCM, 60:40). Found: C, 63.82; H, 4.91; N, 19.71. $C_{15}H_{14}N_4S$ requires: C, 63.80; H, 5.00; N, 19.84%. λ_{max} (DCM) 265 (log ε 4.62), 293 (4.56), 393 (4.21); ν_{max}/cm^{-1} 2990w, 2978w and 2938w (CH_3), 2214m (C≡N), 1560m, 1508m, 1481m, 1464m, 1404m, 1395m, 1368m, 1344m, 1325w, 1298w, 1283m, 1271w, 1246m, 1231m, 1196w, 1179w, 1159m, 1128m, 1105w, 1098w, 1074w, 1030m, 1022m, 937w, 914m, 878w, 849m, 799m, 770m, 739s; δ_H (500 MHz; $CDCl_3$) 8.03 (2H, d, *J* 7.5), 7.51 (2H, dd, *J* 7.8, 7.8), 7.41 (1H, dd, *J* 7.5, 7.5), 1.79 (9H, s); δ_C (125 MHz; $CDCl_3$) 165.4 (s), 136.5 (s), 131.4 (s), 129.0 (d), 128.8 (d), 128.6 (s), 126.7 (d), 119.9 (s), 111.6 (s), 60.3 (s), 28.8 (q); MALDI-TOF MS (*m*/*z*) 283 (MH^+, 96%), 282 (M^+, 49), 227 (100).

*4.6.15. 4-Methyl-6-phenyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5i**).* Procedure A: 41.5 mg, 36%. Procedure B: 7 mg, 6%. Chromatography eluent: *n*-hexane/DCM, 80:20. Yellow needles; mp 145−145.5 °C (from *c*-hexane); R_f 0.48 (*n*-hexane/DCM, 60:40). Found: C, 60.04; H, 3.45; N, 23.12. $C_{12}H_8N_4S$ requires: C, 59.98; H, 3.36; N, 23.32%. λ_{max} (DCM) 257 (log ε 3.80), 290 (3.36), 295 inf (3.34), 396 (2.98); ν_{max}/cm^{-1} 3071w (Ar CH), 2924w (CH_3), 2218 (C≡N), 1591m, 1578m, 1514s, 1501m, 1487m, 1474w, 1445m, 1425m, 1387m, 1341m, 1283m, 1152w, 1117m, 1101m, 1070m, 1059w, 1030w, 1016w, 997w, 903m, 870w, 831w, 752s; δ_H (500 MHz; acetone-d_6) 8.13 (2H, d, *J* 8.0), 7.54 (2H, dd, *J* 8.0, 8.0), 7.28 (1H, dd, *J* 7.5, 7.5), 2.62 (3H, s); δ_C(125 MHz; $CDCl_3$) 163.2 (s), 138.4 (s), 137.4 (s), 132.3 (s), 129.3 (d), 125.3 (d), 120.8 (s), 117.1 (d), 110.0 (s), 13.2 (q); *m*/*z* (EI) 240 (M^+, 100%), 225 (6), 214 (5), 199 (8), 129 (5), 118 (28), 91 (20), 77 (49), 64 (9), 51 (40).

*4.6.16. 4,6-Diphenyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5j**).* Procedure A: 49.5 mg, 34%. Procedure B: 27.5 mg, 19%. Chromatography eluent: *n*-hexane/DCM, 90:10. Yellow needles; mp 152.5−154 °C (from *c*-hexane); R_f 0.60 (*n*-hexane/DCM, 60:40). Found: C, 67.65; H, 3.25; N, 18.46. $C_{17}H_{10}N_4S$ requires: C, 67.53; H, 3.33; N, 18.53%. λ_{max} (DCM) 246 (log ε 3.48), 278 (3.67), 414 (2.99); ν_{max}/cm^{-1} 3067w (Ar CH), 2218m (C≡N), 1597m, 1566m, 1514m, 1501s, 1464m, 1450w, 1420m, 1348m, 1306w, 1281m, 1186w, 1163w, 1136s, 1126m, 1101w, 1072m, 1028w, 1013m, 968w, 918w, 901m, 833m, 773m; δ_H (500 MHz; $CDCl_3$) 8.26 (2H, d, *J* 8.0), 8.14 (2H, d, *J* 7.5), 7.58−7.48 (5H, m), 7.30 (1H, dd, *J* 7.5, 7.5); δ_C (125 MHz; $CDCl_3$) one C (s) resonance missing 163.8 (s), 139.4 (s), 138.4 (s), 130.4 (s), 129.8 (d), 129.4 (d), 129.1 (d), 127.1 (d), 125.8 (d), 121.9 (s), 117.7 (d), 111.0 (s); *m*/*z* (EI) 302 (M^+, 100%), 276 (4), 225 (4), 180 (5), 153 (9), 151 (5), 103 (5), 91 (4), 77 (77), 70 (8), 51 (32).

4.7. 1*H*-Pyrazolo[3,4-*d*]thiazole-5-carbonitriles 4 (General Procedure). A stirred sample of the appropriate neat *N*-(dithiazolylidene)pyrazolamine **3** (0.1 mmol) under an argon atmosphere was immersed into a preheated Wood's metal bath at temperatures specified in Table 2. After 10−15 min, the reaction mixture was allowed to cool to ca. 20 °C and extracted with DCM (3 × 1 mL). The combined extracts were adsorbed onto silica and chromatographed.

*4.7.1. 1,3-Dimethyl-1H-pyrazolo[3,4-d]thiazole-5-carbonitrile (**4a**).* Chromatography eluent: DCM/*t*-BuOMe, 90:10. Colorless needles (13.7 mg, 77%); mp 99−100.5 °C (from *c*-hexane); R_f 0.20 (DCM). Found: C, 47.29; H, 3.26; N, 31.34. $C_7H_6N_4S$ requires: C, 47.18; H, 3.39; N, 31.44%. λ_{max} (DCM) 293 (log ε 2.80), 316 inf (2.32); ν_{max}/cm^{-1} 2941w (CH_3), 2224m (C≡N), 1551m, 1497m, 1452m, 1420m, 1389s, 1356m, 1271w, 1233m, 1165m, 1144m, 1099m, 1047m, 993w, 926w, 837w, 810w, 781w; δ_H (500 MHz; $CDCl_3$) 4.07 (3H, s), 2.47 (3H, s); δ_C (125 MHz; $CDCl_3$) 159.0 (s), 139.2 (s), 137.9 (s), 114.6 (s), 113.0 (s), 36.1 (q), 13.9 (q); *m*/*z* (EI) 178 (M^+, 100%), 163 (15), 85 (94), 70 (86), 58 (8).

*4.7.2. 1-Methyl-3-phenyl-1H-pyrazolo[3,4-d]thiazole-5-carbonitrile (**4d**).* Chromatography eluent: DCM. Colorless needles (19.9 mg, 83%); mp (DSC) onset, 170.5 °C; peak max, 171.3 °C (from *c*-hexane); R_f 0.53 (DCM). Found: C, 59.90; H, 3.42; N, 23.29. $C_{12}H_8N_4S$ requires: C, 59.98; H, 3.36; N, 23.32%. λ_{max} (DCM) 260 inf (log ε 3.33), 264 (3.35), 281 inf (3.24), 295 (3.34), 348 (2.67); ν_{max}/cm^{-1} 3065w, 3042w and 3007w (Ar CH), 2945w (CH_3), 2224m (C≡N), 1545m, 1472s, 1462m, 1452m, 1395m, 1364m, 1356m, 1327w, 1304w, 1292m, 1238m, 1206m, 1182w, 1169w, 1155w, 1121m, 1076w, 1045w, 1030m, 1011m, 912w, 893w, 758s, 731m; δ_H (500 MHz; $CDCl_3$) 7.73 (2H, d, *J* 7.0), 7.43 (2H, dd, *J* 7.5, 7.5), 7.34 (1H, dd, *J* 7.3, 7.3), 4.14 (3H, s); δ_C(125 MHz; $CDCl_3$) 159.4 (s), 141.1 (s), 139.7 (s), 130.8 (s), 129.1 (d), 128.9 (d), 125.6 (d), 112.9 (s), 112.5 (s), 36.6 (q); MALDI-TOF MS (*m*/*z*) 240 (M^+, 100).

*4.7.3. 1-Benzyl-3-methyl-1H-pyrazolo[3,4-d]thiazole-5-carbonitrile (**4e**).* Chromatography eluent: DCM. Colorless prisms (17.5 mg, 69%); mp 91−93 °C (from *n*-pentane at ca. −20 °C); R_f 0.56 (DCM). Found: C, 61.39; H, 3.87; N, 21.84. $C_{13}H_{10}N_4S$ requires: C, 61.40; H, 3.96; N, 22.03%. λ_{max} (DCM) 293 (log ε 4.20), 328 (3.75); ν_{max}/cm^{-1} 3069w, 3034w, 2957w, 2926w, 2230m (C≡N), 1653m, 1533m, 1500m, 1491m, 1456s, 1445m, 1433m, 1389s, 1358m, 1346w, 1331w, 1325w, 1296m, 1273s, 1206m, 1159m, 1148m, 1117m, 1098m, 1076m, 1026w, 1003m, 930m, 910m, 854w, 824m, 772m, 760w, 748w, 741w, 737w, 731w; δ_H (500 MHz; DMSO-d_6) 7.34−7.25 (5H, m), 5.54 (2H, s), 2.42 (3H, s); δ_C (125 MHz; DMSO-d_6) 158.1 (s), 139.6 (s), 138.4 (s), 136.5 (s), 128.8 (d), 128.0 (d), 127.7 (d), 115.3 (s), 113.4 (s), 52.7 (d), 13.6 (q). MALDI-TOF MS (*m*/*z*) 255 (MH^+, 100), 242 (15), 91 (55).

*4.7.4. 1-Benzyl-3-phenyl-1H-pyrazolo[3,4-d]thiazole-5-carbonitrile (**4f**).* Chromatography eluent: *n*-hexane/DCM, 50:50. Beige needles (26.9 mg, 85%); mp 113.5−114.5 °C (from *c*-hexane); R_f 0.50 (*n*-hexane/DCM, 50:50). Found: C, 68.24; H, 3.87; N, 17.77. $C_{18}H_{12}N_4S$ requires: C, 68.33; H, 3.82; N, 17.71%. λ_{max} (DCM) 264 inf (log ε 4.27), 268 (4.28), 297 (4.21), 350 (3.59); ν_{max}/cm^{-1} 3059w, 3032w, and 3009w (Ar CH), 2983w and 2938w (CH_2), 2226m (C≡N), 1530m, 1497m, 1472s, 1460m, 1456m, 1447m, 1427m, 1395m, 1354m, 1344w, 1323w, 1290m, 1279m, 1200m, 1163w, 1153w, 1119s, 1076m, 1032w, 1011m, 993w, 972w, 937w, 922w, 891w, 820w, 773s; δ_H(500 MHz; $CDCl_3$) 7.82 (2H, d, *J* 7.0), 7.49 (2H, dd, *J* 7.8, 7.8), 7.44−7.38 (3H, m), 7.37−7.29 (3H, m), 5.66 (2H, s); δ_C (125 MHz; $CDCl_3$) 158.9 (s), 141.4 (s), 139.9 (s), 135.5 (s), 130.8 (s), 129.1 (d), 128.9 (d), 128.8 (d), 128.4 (d), 128.1 (d), 125.7 (d), 112.9 (s), 54.0 (t); MALDI-TOF MS (*m*/*z*) 317 (MH^+, 100%), 91 (90).

*4.7.5. 3-Methyl-1-phenyl-1H-pyrazolo[3,4-d]thiazole-5-carbonitrile (**4g**).* Chromatography eluent: *n*-hexane/DCM, 50:50. Beige plates (19.9 mg, 83%); mp 127−128.5 °C (from *c*-hexane); R_f 0.50 (*n*-hexane/DCM, 50:50). Found: C, 59.96; H, 3.27; N, 23.29. $C_{12}H_8N_4S$ requires: C, 59.98; H, 3.36; N, 23.32%. λ_{max} (DCM) 247 (log ε 3.41), 294 (3.33), 354 (2.88); ν_{max}/cm^{-1} 2926w (CH_3), 2224m (C≡N), 1593m, 1518s, 1495m, 1464m, 1443m, 1391m, 1381m, 1362m, 1335w, 1317w, 1246w, 1167m, 1144s, 1101m, 1074m, 1043w, 1026w, 1005w, 903m, 868w, 760s, 754s; δ_H (500 MHz; $CDCl_3$) 8.12 (2H, d, *J* 8.0), 7.51 (2H, dd, *J* 8.0, 8.0), 7.31 (1H, dd, *J* 7.3, 7.3), 2.59 (3H, s); δ_C (125 MHz; $CDCl_3$) 157.1 (s), 139.6 (s), 139.5 (s), 138.5 (s), 129.4 (d), 126.4 (d), 118.7 (d), 117.5 (s), 112.9 (s), 14.1 (q); MALDI-TOF MS (*m*/*z*) 241 (MH^+, 100%), 205 (18).

*4.7.6. 1,3-Diphenyl-1H-pyrazolo[3,4-d]thiazole-5-carbonitrile (**4h**).* Chromatography eluent: *n*-hexane/DCM, 60:40. Yellow needles (23.6 mg, 78%); mp (DSC) onset, 185.2 °C; peak max, 185.6 °C (from *c*-hexane); R_f 0.46 (*n*-hexane/DCM, 70:30). Found: C, 67.44; H, 3.18; N, 18.40. $C_{17}H_{10}N_4S$ requires: C, 67.53; H, 3.33; N, 18.53%. λ_{max} (DCM) 239 (log ε 3.37), 278 (3.64), 288 inf (3.61), 371 (3.00); ν_{max}/cm^{-1} 3061w (Ar CH), 2226m (C≡N), 1595m, 1514s, 1487m, 1476m, 1460m, 1445w, 1393w, 1362s, 1331w, 1321m, 1287m, 1213w,

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1163w, 1150m, 1128w, 1098w, 1076m, 1024w, 1001m, 989m, 916w, 908w, 772m, 758s, 729m; δ_H (500 MHz; $CDCl_3$) 8.26 (2H, dd, *J* 8.5, 1.0), 7.93 (2H, dd, *J* 8.0, 1.0), 7.58−7.53 (4H, m), 7.46 (1H, dd, *J* 7.3, 7.3), 7.36 (1H, dd, *J* 7.5, 7.5); δ_C (125 MHz; $CDCl_3$) one C (s) resonance missing 142.0 (s), 140.1 (s), 138.6 (s), 130.3 (s), 129.5 (d), 129.4 (d), 129.2 (d), 126.8 (d), 126.0 (d), 119.0 (d), 115.3 (s), 112.8 (s); MALDI-TOF MS (*m*/*z*) 303 (MH^+, 92%), 302 (M^+, 100).

4.8. Debenzylation Reactions with Br_2/AIBN. *4.8.1. 3-Phenyl-1H-pyrazolo[4,3-d]thiazole-5-carbonitrile (**4c**) (Typical Procedure).* A stirred mixture of 1-benzyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitrile (**4f**) (31.6 mg, 0.1 mmol), dibromine (7.7 μL, 0.15 mmol), AIBN (3.3 mg, 0.02 mmol), and PhH/H_2O (2:1, 1.5 mL) was heated to ca. 80 °C for 2 h. The reaction mixture was then allowed to cool to ca. 20 °C, additional dibromine (7.7 μL, 0.15 mmol) and AIBN (3.3 mg, 0.02 mmol) were added, and the mixture was heated again to ca. 80 °C for a further 5 h. The reaction mixture was then allowed to cool to ca. 20 °C, and the volatiles were removed in vacuo. To the remaining residue was added a solution of NaOH in EtOH (2 mL, 0.05 M), and the mixture was heated to ca. 78 °C for 12 h. The reaction mixture was then allowed to cool to ca. 20 °C, adsorbed onto silica, and chromatographed (DCM/*t*-BuOMe, 90:10) to give the title compound **4c** (17.2 mg, 76%) as colorless cotton fibers; mp 191−193 °C (from *c*-hexane/$CHCl_3$); R_f 0.57 (DCM/*t*-BuOMe, 90:10). Found: C, 58.51; H, 2.73; N, 24.88. $C_{11}H_6N_4S$ requires: C, 58.39; H, 2.67; N, 24.76%. λ_{max} (DCM) 258 inf (log ε 4.30), 262 (4.31), 290 (4.34), 325 inf (3.75); ν_{max}/cm^{-1} 3105w, 3024w and 2895w (NH), 2234w (C≡N), 1501m, 1474m, 1437s, 1387w, 1314m, 1298m, 1184m, 1125s, 1096w, 1001w, 986m, 901w, 818m, 756s; δ_H (500 MHz; acetone-d_6) NH resonance missing 7.91 (2H, d, *J* 7.0), 7.57 (2H, dd, *J* 7.8, 7.8), 7.46 (1H, dd, *J* 7.5, 7.5); δ_C (125 MHz; TFA-*d*) 160.7 (s), 149.5 (s), 144.2 (s), 134.4 (d), 131.8 (d), 128.4 (d), 126.1 (s), 115.6 (s), 111.7 (s); MALDI-TOF MS (*m*/*z*) 227 (MH^+, 100%).

*4.8.2. 4-Methyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5b**).* Similar treatment of 6-benzyl-4-methyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5e**) (25.4 mg, 0.1 mmol) gave the title compound **5b** (3.1 mg, 19%) as colorless needles; mp 182−183.5 °C (from *c*-hexane/$CHCl_3$); R_f 0.33 (DCM/*t*-BuOMe, 97:3); identical to that described above.

*4.8.3. 4-Phenyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5c**).* Similar treatment of 6-benzyl-4-phenyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5f**) (31.6 mg, 0.1 mmol) gave the title compound **5c** (20.8 mg, 92%) as pale yellow needles; mp 196−197 °C (from *c*-hexane/$CHCl_3$); R_f 0.68 (DCM/*t*-BuOMe, 96:4); identical to that described above.

4.9. Hydration of 1*H*-Pyrazolo[3,4-*d*]thiazole-5-carbonitriles 4e and 4f and 6*H*-Pyrazolo[3,4-*c*]isothiazole-3-carbonitriles 5f and 5h. *4.9.1. 6-Benzyl-4-phenyl-6H-pyrazolo[3,4-c]isothiazole-3-carboxamide (**19a**) (Typical procedure).* A stirred solution of 6-benzyl-4-phenyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5f**) (31.6 mg, 0.1 mmol) in AcOH (2 mL) was heated to ca. 118 °C for 3 d. The reaction mixture was allowed to cool to ca. 20 °C, poured onto crushed ice, neutralized (sat. $NaHCO_3$), and extracted with *t*-BuOMe (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue obtained was dissolved in DCM (10 mL), adsorbed onto silica, and chromatographed to give the title compound **19a** (27.8 mg, 83%), as pale yellow needles; mp 181−183 °C (from *c*-hexane/$CHCl_3$); R_f 0.50 (DCM/*t*-BuOMe, 90:10). Found: C, 64.56; H, 4.21; N, 16.62. $C_{18}H_{14}N_4OS$ requires: C, 64.65; H, 4.22; N, 16.75%. λ_{max} (DCM) 258 (log ε 3.97), 289 (3.89), 369 (3.71); ν_{max}/cm^{-1} 3451m, 3439m, 3331w, 3273w and 3130m (NH_2), 2931w (CH_2), 1670s (C=O), 1659m, 1607m, 1572m, 1514w, 1495w, 1477m, 1454m, 1435m, 1412m, 1391m, 1358w, 1352w, 1327m, 1308m, 1273m, 1206w, 1182w, 1157w, 1134m, 1109m, 1076m, 1070m, 1042w, 1022m, 934m, 924m, 887m, 845m, 839m, 791m, 779m, 770m, 758m; δ_H (500 MHz; $CDCl_3$) 7.71 (2H, d, *J* 8.0), 7.52−7.46 (3H, m), 7.43 (2H, d, *J* 7.5), 7.33 (2H, dd, *J* 7.5, 7.5), 7.29 (1H, dd, *J* 7.3, 7.3), 5.75 (2H, br s), 5.50 (2H, s); δ_C(125 MHz; $CDCl_3$) one C (d) resonance missing 166.6 (s), 161.0 (s), 150.9 (s), 138.2 (s), 136.1 (s), 131.8 (s), 129.5 (d), 129.0 (d), 128.7 (d), 128.13 (d), 128.06 (d), 121.8 (s), 52.3 (t); MALDI-TOF MS (*m*/*z*) 335 (MH^+, 100%), 333 ($M^+ - 1$, 27), 324 (31), 318 (28), 292 (15), 281 (13), 257 (10), 90 (67).

*4.9.2. 6-(tert-Butyl)-4-phenyl-6H-pyrazolo[3,4-c]isothiazole-3-carboxamide (**19b**).* Similar treatment of 6-(*tert*-butyl)-4-phenyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5h**) (28.2 mg, 0.1 mmol) gave the title compound **19b** (23.7 mg, 83%), as pale yellow needles; mp 197.5−198.5 °C (from *c*-hexane/$CHCl_3$); R_f 0.43 (DCM/Et_2O, 90:10). Found: C, 59.86; H, 5.26; N, 18.74. $C_{15}H_{16}N_4OS$ requires: C, 59.98; H, 5.37; N, 18.65%. λ_{max} (DCM) 260 (log ε 4.13), 290 (4.10), 373 (3.89); ν_{max}/cm^{-1} 3462m, 3269m, and 3173m (NH), 2980m and 2932w (CH_3), 1665m, 1639s (C=O), 1611m, 1568m, 1510w, 1466m, 1439w, 1383s, 1329m, 1300w, 1283w, 1263m, 1242m, 1182m, 1134s, 1094m, 1074w, 1020m, 986w, 926m, 914m, 872m, 845m, 804m, 773s, 748s; δ_H (500 MHz; $CDCl_3$) 7.71 (2H, d, *J* 7.0), 7.50 (2H, dd, *J* 7.3, 7.3), 7.45 (1H, dd, *J* 7.3, 7.3), 6.15 (1H, br s), 5.66 (1H, br s), 1.78 (9H, s); δ_C (125 MHz; $CDCl_3$) 166.3 (s), 161.5 (s), 149.1 (s), 136.3 (s), 132.3 (s), 129.2 (d), 128.9 (d), 128.8 (d), 122.9 (s), 59.8 (s), 28.9 (q); MALDI-TOF MS (*m*/*z*) 301 (MH^+, 100%), 245 (80).

*4.9.3. 1-Benzyl-3-methyl-1H-pyrazolo[3,4-d]thiazole-5-carboxamide (**21a**).* Similar treatment of 1-benzyl-3-methyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitrile (**4e**) (25.4 mg, 0.1 mmol) with concd H_2SO_4 (1 mL) at ca. 20 °C for 2 h gave the title compound **21a** as colorless needles (23.1 mg, 85%); mp 159−161 °C (from *c*-hexane/$CHCl_3$); R_f 0.29 (DCM/Et_2O, 90:10). Found: C, 57.29; H, 4.31; N, 20.46. $C_{13}H_{12}N_4OS$ requires: C, 57.34; H, 4.44; N, 20.57%. λ_{max} (EtOH) 209 (log ε 4.15), 288 (4.02), 316 (3.71); ν_{max}/cm^{-1} 3470m, 3347w, 3275w, and 3196m (NH_2), 1688s (C=O), 1585m, 1531m, 1501m, 1485m, 1460m, 1402m, 1377m, 1356w, 1333w, 1319w, 1288w, 1271m, 1204w, 1153m, 1119m, 1070m, 1034w, 1007w, 941w, 924w, 908w, 818w, 766m, 731m; δ_H (500 MHz; DMSO-d_6) 8.32 (1H, s), 8.04 (1H, s), 7.33 (2H, dd, *J* 7.3, 7.3), 7.29−7.26 (3H, m), 5.52 (2H, s), 2.39 (3H, s); δ_C (125 MHz; DMSO-d_6) 169.0 (s), 161.2 (s), 158.5 (s), 138.1 (s), 136.9 (s), 128.5 (d), 127.6 (d), 127.3 (d), 114.1 (s), 52.1 (t), 13.5 (q); MALDI-TOF MS (*m*/*z*) 273 (MH^+, 82%), 257 (22), 229 (7), 91 (100).

*4.9.4. 1-Benzyl-3-phenyl-1H-pyrazolo[3,4-d]thiazole-5-carboxamide (**21b**).* Similar treatment of 1-benzyl-3-methyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitrile (**4f**) (25.4 mg, 0.1 mmol) with concd H_2SO_4 (1 mL) at ca. 20 °C for 2 h gave the title compound **21b** as colorless, cotton-like fibers (29.4 mg, 88%); mp 204−205 °C (from *c*-hexane/$CHCl_3$); R_f 0.48 (DCM/Et_2O, 90:10). Found: C, 64.57; H, 4.16; N, 16.66. $C_{18}H_{14}N_4OS$ requires: C, 64.65; H, 4.22; N, 16.75%. λ_{max} (DCM) 265 (log ε 4.35), 295 (4.19), 334 inf (3.77); ν_{max}/cm^{-1} 3447m and 3150m (NH_2), 1690s (C=O), 1595m, 1533m, 1489m, 1452m, 1412m, 1383m, 1360m, 1331m, 1296m, 1281m, 1202w, 1175w, 1155w, 1123m, 1074m, 1013m, 991w, 945m, 920w, 908w, 889w, 835w, 772m, 766m, 733s; δ_H(500 MHz; DMSO-d_6) 8.44 (1H, s), 8.13 (1H, s), 7.83 (2H, d, *J* 7.5), 7.52 (2H, dd, *J* 7.8, 7.8), 7.41 (1H, dd, *J* 7.3, 7.3), 7.36−7.34 (4H, m), 7.32−7.28 (1H, m), 5.69 (2H, s); δ_C (125 MHz; DMSO-d_6) one C (s) resonance missing 169.9 (s), 161.0 (s), 159.1 (s), 140.5 (s), 136.5 (s), 131.0 (s), 129.1 (d), 128.6 (d), 128.4 (d), 127.8 (d), 127.4 (d), 125.1 (d), 112.0 (s), 52.7 (t); MALDI-TOF MS (*m*/*z*) 335 (MH^+, 100%), 318 (7), 292 (6), 91 (72).

4.10. *N*-Debenzylation/Debutylation Reactions Using Concentrated H_2SO_4. General Procedure: To stirred, concd H_2SO_4 (1 mL) at ca. 20 °C the appropriate 6*H*-pyrazolo[3,4-*c*]isothiazole-3-carbonitrile (**5e**−**5h**) (0.1 mmol) was added in one portion. The reaction mixture was then placed in a preheated oil bath at ca. 60 °C and stirred at this temperature until completion of the reaction (by TLC), after which the reaction mixture was allowed to cool to ca. 20 °C, poured onto crushed ice, and neutralized (sat. $NaHCO_3$). The aqueous phase was extracted with *t*-BuOMe (3 × 20 mL), the combined organic phase was dried (Na_2SO_4), and the volatiles were removed in vacuo. The residue was dissolved in THF/EtOH 1:1 (10 mL), adsorbed onto silica, and chromatographed. See Scheme 10 for yields and reaction times.

*4.10.1. 4-Methyl-6H-pyrazolo[3,4-c]isothiazole-3-carboxamide (**20a**).* Beige plates; mp (DSC) onset, 239.5 °C; peak max, 248.4

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°C; dec onset, 250.2 °C; peak max, 251.2 °C (from EtOH); R_f 0.35 (Et_2O). Found: C, 39.56; H, 3.23; N, 30.69. $C_6H_6N_4OS$ requires: C, 39.55; H, 3.32; N, 30.75%. λ_{max} (EtOH) 229 (log ε 3.21), 284 (3.74), 341 (3.60); ν_{max}/cm^{-1} 3455m, 3261m, and 3183m (NH and NH_2), 1651s (C═O), 1585m, 1572m, 1510w, 1493m, 1431m, 1381m, 1294m, 1132w, 1078m, 1042m, 991m, 928m, 841w, 795m, 768m, 752w; δ_H(500 MHz; DMSO-d_6) 12.55 (1H, s), 8.09 (1H, br s), 7.89 (1H, br s), 2.44 (3H, s); δ_C (125 MHz; DMSO-d_6) 167.5 (s), 160.8 (s), 149.8 (s), 137.1 (s), 126.5 (s), 14.4 (q); MALDI-TOF MS (m/z) 181 ($M^+ - 1$, 100%), 138 (3).

*4.10.2. 4-Phenyl-6H-pyrazolo[3,4-c]isothiazole-3-carboxamide (**20b**).* Pale yellow plates; mp 261−262 °C (from EtOH); R_f 0.62 (DCM/*t*-BuOMe, 70:30), Found: C, 54.20; H, 3.17; N, 22.86. $C_{11}H_8N_4OS$ requires: C, 54.09; H, 3.30; N, 22.94%. λ_{max} (EtOH) 206 (log ε 4.17), 254 (4.12), 278 (4.13), 346 (3.90); ν_{max}/cm^{-1} 3464w, 3343w, 3287w (NH and NH_2), 2833w, 1655m, 1651m, 1589m, 1497w, 1464w, 1437m, 1371m, 1323m, 1302m, 1277m, 1169w, 1105m, 1072m, 1034m, 1015m, 914m, 858m, 783s, 739m; δ_H (500 MHz; DMSO-d_6) 13.24 (1H, br s), 8.19 (1H, br s), 8.09 (1H, br s), 7.83 (2H, dd, *J* 8.5, 1.5), 7.45 (2H, dd, *J* 7.5, 7.5), 7.39 (1H, dd, *J* 7.3, 1.3); δ_C (125 MHz; DMSO-d_6) 167.5 (s), 161.7 (s), 151.2 (s), 139.1 (s), 132.2 (s), 128.52 (d), 128.47 (d), 127.4 (d), 122.7 (s); MALDI-TOF MS (m/z) 246 (MH^++1, 42%), 245 (MH^+, 100), 228 (54).

4.11. Dehydration Reactions with $POCl_3$. *4.11.1. 4-Methyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5b**) (Typical Procedure).* To stirred $POCl_3$ (3 mL) at ca. 20 °C was added in one portion 4-methyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carboxamide (**20a**) (18.2 mg, 0.1 mmol). The reaction mixture was then placed in a preheated oil bath at ca. 60 °C for 4.5 h. The reaction mixture was then allowed to cool to ca. 20 °C, poured onto crushed ice, neutralized (sat. $NaHCO_3$), and extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue obtained was dissolved in DCM, adsorbed onto silica and chromatographed (DCM/*t*-BuOMe, 90:10) to give the title compound **5b** (13.9 mg, 85%) as colorless needles; 182−183.5 °C (from *c*-hexane/$CHCl_3$); R_f 0.33 (DCM/*t*-BuOMe, 97:3); identical to that described above.

*4.11.2. 4-Phenyl-6H-pyrazolo[3,4-c]isothiazole-3-carbonitrile (**5c**).* Similar treatment of 4-phenyl-6*H*-pyrazolo[3,4-*c*]isothiazole-3-carboxamide (**20b**) (24.4 mg, 0.1 mmol) gave the title compound **5c** (20.7 mg, 92%) as pale yellow needles; mp 196−197 °C (from *c*-hexane/$CHCl_3$); R_f 0.68 (DCM/*t*-BuOMe, 96:4); identical to that described above.

4.12. X-ray Crystallographic Studies. Data were collected on an Oxford-Diffraction Supernova diffractometer equipped with a CCD area detector utilizing Mo Kα radiation (λ = 0.71073 Å). A suitable crystal was attached to glass fibers using paratone-N oil and transferred to a goniostat where they were cooled for data collection. Unit cell dimensions were determined and refined by using 6074 ($3.02 \leq \theta \leq 28.90°$) reflections for **5a** and **11** and 5674 ($3.40 \leq \theta \leq 26.97°$) reflections for **12**. Empirical absorption corrections (multiscan based on symmetry-related measurements) were applied using CrysAlis RED software.[39] The structure was solved by direct methods using SIR92[40] and refined on F^2 using full-matrix least-squares using SHELXL-97.[41] The following software packages were used: CrysAlis CCD[39] for data collection, CrysAlis RED[39] for cell refinement and data reduction, WINGX for geometric calculations,[42] and DIAMOND[43] for molecular graphics. The non-H atoms were treated anisotropically. The hydrogen atom attached to N3 was located on a difference Fourier map, whereas all other hydrogen atoms were placed in calculated, ideal positions and refined as riding on their respective carbon atoms.

*4.12.1. Crystal Refinement Data for Compound **5a**.* $C_7H_6N_4S$, M = 178.18, triclinic, space group $P\bar{1}$, a = 3.8592(3) Å, b = 8.404(2) Å, c = 12.541(2) Å, α = 87.52(2)°, β = 85.342(9)°, γ = 81.578(9)°, V = 400.83(8) Å^3, Z = 2, T = 100(2) K, ρ_{calcd} = 1.477 g cm^{-3}, $2\theta_{max}$ = 24.99, μ(Mo Kα) = 0.347 mm^{-1}. Reflections measured, 2255; independent reflections, 1417 (R_{int} = 0.0381). The final R_1 and $wR(F^2)$ values were 0.0508 and 0.1434 [$I > 2\sigma(I)$], respectively. The goodness of fit on F^2 was 0.903.

*4.12.2. Crystal Refinement Data for Compound **11**.* $C_{14}H_{12}Cl_2N_8S_5$, M = 523.57, monoclinic, space group $C2/c$, a = 34.721(5) Å, b = 4.0036(5) Å, c = 14.975(2) Å, β = 100.148(13)°, V = 2049.1(5) Å^3, Z = 4, T = 100(2) K, ρ_{calcd} = 1.697 g cm^{-3}, $2\theta_{max}$ = 26.5, μ(Mo Kα) = 0.847 mm^{-1}. Reflections measured, 4564; independent reflections, 2101 (R_{int} = 0.0575). The final R_1 and $wR(F^2)$ values were 0.0623 and 0.1812 [$I > 2\sigma(I)$], respectively. The goodness of fit on F^2 was 1.035.

*4.12.3. Crystal Refinement Data for Compound **12**.* $C_{16}H_{14}Cl_3N_9S_5$, M = 599.06, triclinic, space group $P\bar{1}$, a = 10.4490(4) Å, b = 12.6255(8) Å, c = 21.3511(9) Å, α = 97.143(4)°, β = 92.352(3)°, γ = 93.441(4)°, V = 2786.5(2) Å^3, Z = 4, T = 100(2) K, ρ_{calcd} = 1.428 g cm^{-3}, $2\theta_{max}$ = 25, μ(Mo Kα) = 0.727 mm^{-1}. Reflections measured, 20504; independent reflections, 9786 (R_{int} = 0.0575). The final R_1 and $wR(F^2)$ values were 0.0824 and 0.2523 [$I > 2\sigma(I)$], respectively. The goodness of fit on F^2 was 1.000.

Crystallographic data for compounds **5a**, **11**, and **12** has been deposited with the Cambridge Crystallographic Data Centre under deposit numbers CCDC-984832, 984833, and 984834, respectively. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax, +441223336033; or e-mail, deposit@ccdc.cam.ac.uk).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of 1D ^{1}H and ^{13}C NMR spectra of all compounds. Single-crystal X-ray structures of compounds **5a**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

†Dedicated to the memory of Professor Alan R. Katritzky, who passed away on February 10, 2014.

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