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Transformation of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile into 4-aminopyrido[2,3-*d*]pyrimidines and 2-(pyrid-2-yl)guanidines

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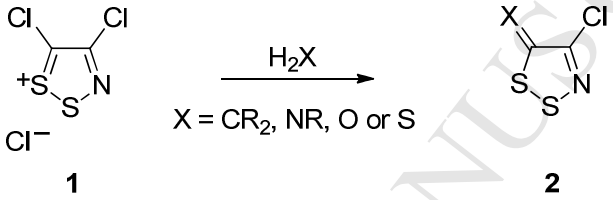
Abstract. The reactions of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**14**) with a range of primary and secondary amines are investigated. Treatment with *n*-$BuNH_2$ and $BnNH_2$ gave 1,3-di-*n*-butyl- and 1,3-dibenzyl-2-(3,5-dicyano-6-ethoxy-4-phenylpyrid-2-yl)guanidines **15a** (32%) and **15b** (82%), respectively. While treatment with Et_2NH, *n*-Pr_2NH or Bn_2NH gave the analogous 4-dialkylaminopyrido[2,3-*d*]pyrimidines **16c-e** in high yields. Treatment of the dithiazole **14** with pyrrolidine, piperidine or morpholine gave the analogous 4-dialkylaminopyrido[2,3-*d*]pyrimidines **16f-h**, the 2-aminopyridine **13** and 2-(diamino-1-ylmethyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitriles **15f-h**. The 4-dialkylaminopyrido[2,3-*d*]pyrimidines **16f-h** are converted to the 2-(dialkylamino-1-ylmethyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitriles **15f-h** upon further reaction with excess dialkylamines. The structure and origins of the two side products **17** and **18** is also discussed. Tentative mechanisms for these transformations are proposed.

Keywords: Fused heterocycles; ring transformations; guanidines; pyridines; pyrimidines; sulfur-nitrogen heterocycles.

1. Introduction

4,5-Dichloro-1,2,3-dithiazolium chloride (**1**) (Appel salt)[1] was prepared 30 years ago and its chemistry has been exploited extensively to prepare many neutral 5*H*-1,2,3-dithiazoles *e.g.*, compounds **2**, where X = CR_2, NR, O or S (Scheme 1). Some of these dithiazoles show interesting biological activity as fungicides,[2] herbicides,[3] or as antibacterials,[4] while more recent studies revealed antitumor activity[5] and inactivation of the glutamine/amino acid transporter ASCT2.[6] 1,2,3-Dithiazolyls are also of interest in the materials sciences as potential conductors and as organic magnets.[7]

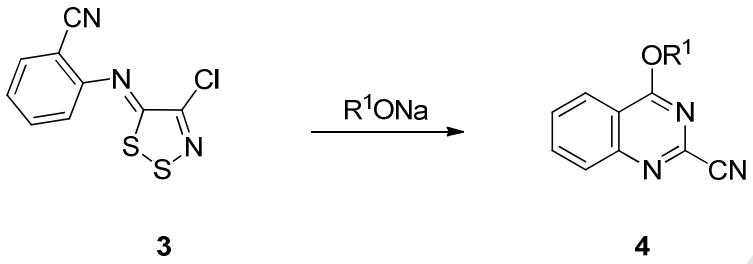


Scheme 1

Neutral 4-chloro-1,2,3-dithiazoles are useful for the preparation of a plethora of cyano substituted heteroarenes. In particular, *N*-substituted 1,2,3-dithiazolylideneamines have been converted to benzothiazoles,[8] benzimidazoles,[9] thiazolopyridines,[10] and benzoxazines,[11] while selected 1,2,3-dithiazolylideneacetonitriles have been converted into isothiazoles[12] and the rare 3*H*-pyrrole system.[13] Acyclic functionalities such as isothiocyanates[14] and thiocyano-formamides[15] can also be prepared from neutral 1,2,3-dithiazolylideneamines. Several excellent reviews on 1,2,3-dithiazoles have appeared.[16]

Quinazoline-2-carbonitriles are important heterocycles that can be accessed from 2-cyano-(1,2,3-dithiazolylideneamino)arenes; quinazolines are present in many pharmaceuticals like the antihypertensive drug Prazosin,[17] the 5-HT2 antagonist Ketanserin[18] and the antitumor drug trimetrexate.[19] Treatment of readily prepared (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-

ylideneamino)benzonitrile (**3**)[15c] with alkoxides affords 4-alkoxyquinazoline-2-carbonitriles **4** in good yields (Scheme 2).[2c,20]

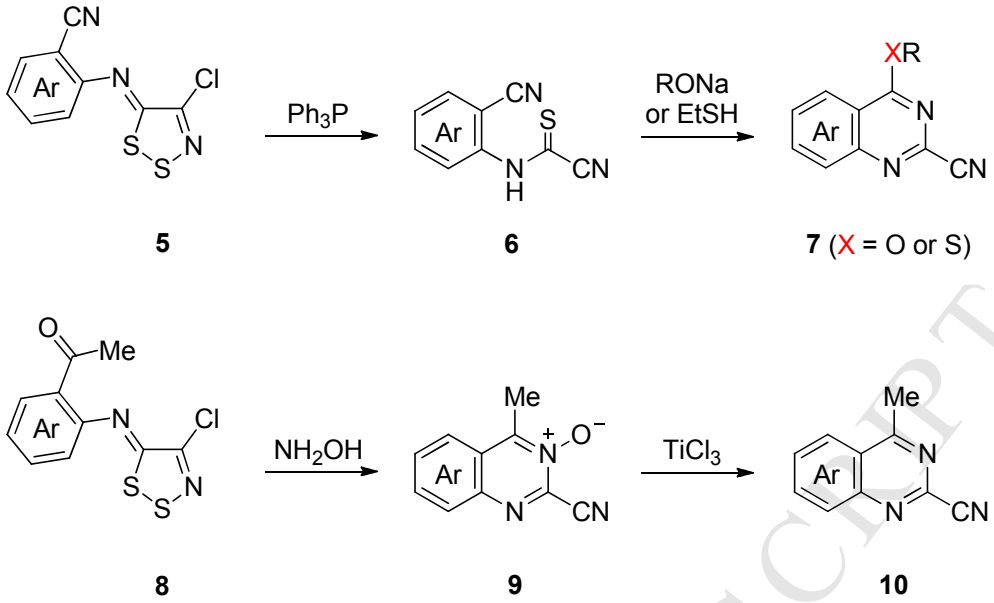


3 **4**

Scheme 2

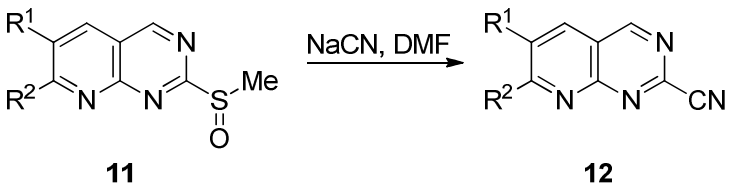
This alkoxide mediated ring transformation of dithiazoles has also been demonstrated with cyano substituted (dithiazolylideneamino)pyrazoles, -imidazoles and -triazoles to afford the corresponding 1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carbonitrile, 9*H*-purine-2-carbonitrile and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-carbonitriles, respectively.[21]

Alternative two step protocols have also been reported where the dithiazole **5** is first converted to the cyanoformanilide **6** by treatment with Ph_3P and subsequent cyclisation induced by alkoxides,[20a,b] or EtSH[2c] affords the quinazolines **7**. This indicated that cyanoformanilides can be intermediates in this ring transformation (Scheme 3). Furthermore, Kim *et al.*,[15a] treated 2-carboxy substituted 2-(dithiazolylideneamino)benzenes **8** initially with hydroxylamine to yield quinazoline *N*-oxides **9**, that on reduction with $TiCl_3$ gave quinazolines **10** (Scheme 3).



Scheme 3

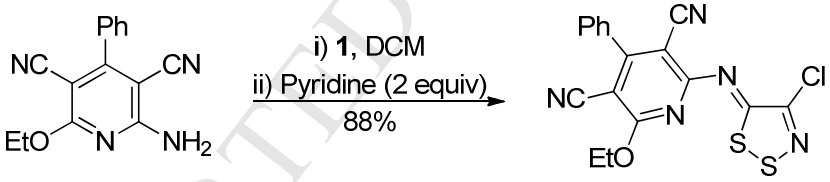
In principle the ring transformation of dithiazoles to quinazolines can be used to prepare pyrido[2,3-*d*]pyrimidine-2-carbonitriles. Selected analogues display potentially useful biological properties, including antitumor activity as potent Akt1/2 inhibitors,[22] and as cannabinoid-1 receptor inverse agonists[23] making them useful as antiobesity agents and as capsaicin receptor modulators.[24] The nitrile group at the 2-position of pyrido[2,3-*d*]pyrimidines is desirable as this can provide access to a wide range of derivatives by hydrolysis,[22b,c] reduction, decarboxylation and reaction with nucleophiles.[25] Until now, the incorporation of the cyano group in pyrido[2,3-*d*]pyrimidine-2-carbonitriles **12** was achieved by substitution from the sulfoxide **11** with cyanide [TOXIC] (Scheme 4).[22b,c] Appel salt **1**, which is an ideal reagent for synthesising cyano-substituted heterocycles,[26] can therefore provide an alternative route to pyrido[2,3-*d*]pyrimidine-2-carbonitriles **12** avoiding the use of cyanides.



Scheme 4

Recently, we explored the synthesis[27] and chemistry of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**14**).[10] We were attracted to this dithiazole by the biological properties and facile synthesis of the precursor amine, 2-amino-3,4-dicyano-5-phenyl-6-ethoxypyridine (**13**). The 2-aminopyridine **13**, readily prepared from benzaldehyde and malononitrile,[28] has a high conductance-type Ca activated K channel opening effect that acts as a smooth muscle relaxant for the bladder making it useful in treating pollakluria and urinary incontinence,[28,29] and derivatives can act as antibacterials.[30] As such, we considered that the dithiazole **14** could be a source of new highly substituted heteroarenes that can be potentially useful small molecule scaffolds.

Herein, we describe the reaction of the dithiazole **14**[27] with primary and secondary amines as nucleophiles which gave polysubstituted pyrido[2,3-*d*]pyrimidine-2-carbonitriles and/or 2-(3,5-dicyano-6-ethoxy-4-phenylpyrid-2-yl)guanidines, as well as other unexpected side products.



13 **14**

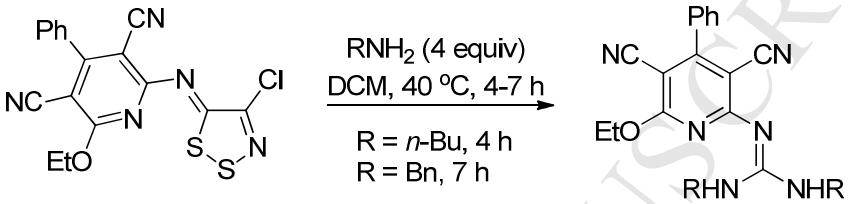
Scheme 5

2. Results and discussion

2.1. Reaction of the dithiazole **14** with amines

To investigate the potential for synthesis of pyrido[2,3-*d*]pyrimidine-2-carbonitriles, the dithiazole **14** was treated with a range of alkyl- and arylamines. Treatment with the primary alkylamines *n*-butylamine or benzylamine (4 equiv) in DCM heated to reflux gave not the

expected 4-alkylaminopyrido[2,3-*d*]pyrimidine-2-carbonitriles but instead 1,3-di-*n*-butyl- and 1,3-dibenzyl-2-(3,5-dicyano-6-ethoxy-4-phenylpyrid-2-yl)guanidines **15a** and **15b** in 32 and 82% yields, respectively (Scheme 6). Treatment with the less nucleophilic primary arylamine aniline (8 equiv) both in DCM and in PhMe, heated at reflux gave no reaction and the starting material was recovered in 89 and 90% yields, respectively. The spectroscopic data for the two compounds **15a** and **15b** agreed with the assigned guanidine structures.



14

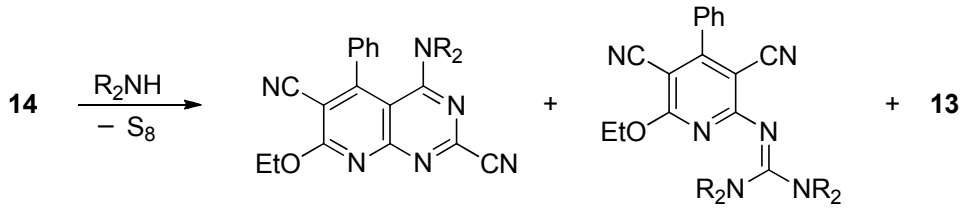
15a (R = *n*-Bu, 32%)
15b (R = Bn, 82%)

Scheme 6

Pyridoguanidines derived from 2-aminopyridine-3-carbonitrile **13** are biologically important compounds since they can inhibit the release of histamine making them potentially useful as antianaphylactic agents,[29a] while other pyridoguanidines have been investigated as urokinase-type plasminogen activator (uPA) inhibitors,[31] and antibacterials against tuberculosis.[32] Their formation in our reaction, was mechanistically intriguing and will be discussed below (see Sect. 2.3).

Fortunately, when the dithiazole **14** was reacted with the secondary dialkylamines Et_2NH, *n*-Pr_2NH and Bn_2NH, the main products were the desired 4-dialkylaminopyrido[2,3-*d*]-pyrimidines **16c-e** in moderate to high yields (Table 1, entries 1-3). Reaction with *i*-Pr_2NH gave an incomplete and complex reaction while reaction with the sterically hindered and less nucleophilic diphenylamine gave no reaction.

Table 1. Reaction of the dithiazole **14** with dialkylamines.



16c-h **15f-h**

Entry	R_2NH (equiv)	Solvent	Temp. (^oC)	Time	S_8	Yields (%) **16**	**15**	**13**
1	Et_2NH (4)	DCM	40	3.5 h	86	**16c** (84)[a]	-	6
2	*n*-Pr_2NH (4)	DCM	40	4 h	97	**16d** (73)	-	-
3	Bn_2NH (20)	PhMe	110	48 h	97	**16e** (50)	-	-
4	pyrrolidine (2)	DCM	40	48 h	94	**16f** (50)	**15f** (12)	9
5	pyrrolidine (2)	PhMe	110	22 h	94	**16f** (76)	**15f** (18)	5
6	pyrrolidine (4)	DCM	40	10 min	95	**16f** (78)	**15f** (14)	6
7	pyrrolidine (20)	DCM	40	5 d	15	**16f** (trace)	**15f** (80)	18
8	piperidine (4)	DCM	40	3.5 h	94	**16g** (74)	**15g** (11)	10
9	piperidine (20)	DCM	40	7 d	45	**16g** (54)	**15g** (18)	16
10	morpholine (4)	DCM	40	13 h	89	**16h** (77)	**15h** (2)	12
11	morpholine (20)	DCM	40	7 d	99	**16h** (25)	**15h** (42)	12

[a] Also isolated: side products **17** and **18** in 5 and 2%, respectively.

Worthy of note, was that at least four equivalents of either Et_2NH and *n*-Pr_2NH were required to fully consume the dithiazole **14** and gave the 4-dialkylaminopyrido[2,3-*d*]pyrimidines **16c** and **16d** in high yields (Table 1, entries 1 and 2). In contrast, the reaction of Bn_2NH required more aggressive conditions to come to completion, as twenty equivalents of amine were used in PhMe, at *ca.* 110 ^oC and gave 4-dibenzylaminopyrido[2,3-*d*]pyrimidine **16e** in a modest 50% yield (Table 1, entry 3). This result can be attributed to the increased steric hindrance from the two benzyl groups that decreased the nucleophilicity of Bn_2NH compared to Et_2NH and *n*-Pr_2NH. The same can be said for *i*-Pr_2NH that has even bulkier isopropyl groups (*A* value for *i*-Pr is 2.15 *vs* 1.75 for Et).[33] The low reactivity of diphenylamine (data not shown) can be attributed to electronic reasons as the two phenyl groups draw electron density away from the amino group, decreasing significantly its nucleophilicity. Interestingly, the reaction

with Et_2NH also led to the formation of 2-[4-(diethylamino)-5*H*-1,2,3-dithiazol-5-ylidene-amino]-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**17**) and the deep green coloured 6,6'-{(1*Z*,1'*Z*)-[(*E*)-4,4'-bis(diethylamino)-5*H*,5'*H*-(2,2'-bithiazolylidene)-5,5'-diylidene]bis-(azanylylidene)}bis(2-ethoxy-4-phenylpyridine-3,5-dicarbonitrile) (**18**) in 5 and 2% yields, respectively; the structure elucidation of the latter was achieved *via* single crystal X-ray crystallography (Figure 1).

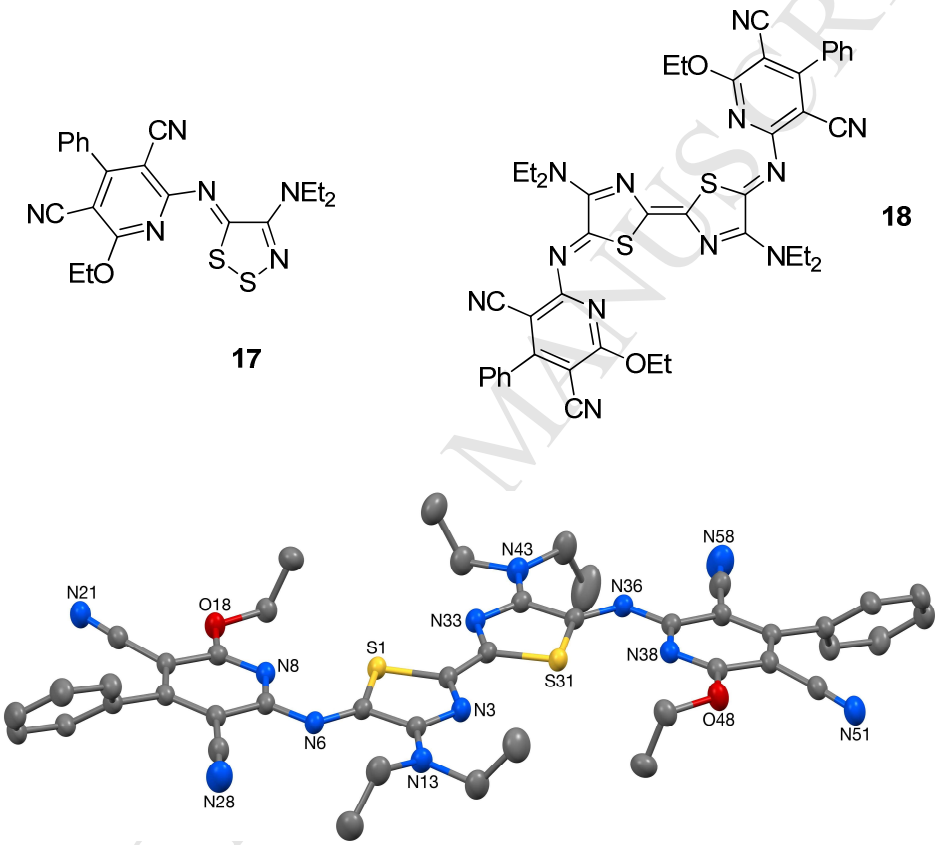


Figure 1. The crystal structure of the quinoidal 2,2'-bithiazole **18** (50% probability ellipsoids and hydrogen atoms omitted for clarity).

Moreover, reacting the dithiazole **14** with either pyrrolidine, piperidine or morpholine gave as main products 4-dialkylaminopyrido[2,3-*d*]pyrimidines **16f-h** along with elemental sulfur and as minor products the 2-aminopyridine **13** and 2-(diamino-1-ylmethyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitriles **15f-h** (Table 1, entries 4-11). The best yields of the

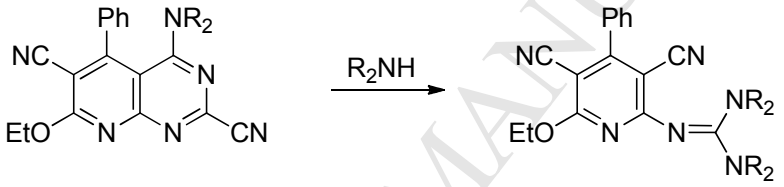
4-dialkylaminopyrido[2,3-*d*]pyrimidines **16f-h** were obtained when four equivalents of base were used in DCM heated at reflux. These reactions had a significant difference in the time needed for each to come to completion: the reaction with pyrrolidine was the fastest (10 min) while the reaction with morpholine was the slowest (13 h), which correlated with the relative nucleophilicity of the amines.[34]

Intrigued by the formation of guanidines **15f-h** we briefly examined conditions for increasing their yields in this reaction: when an excess of dialkylamine (20 equiv) and prolonged reaction times were used (Table 1, entries 7, 9 and 11), the yields of 4-dialkylamino-pyrido[2,3-*d*]pyrimidines **16f-h** decreased while the yields of 2-dialkylaminoguanidino-pyridines **15a-c** increased. The reaction with pyrrolidine after 5 days led to complete consumption of the 4-pyrrolidinopyrido[2,3-*d*]pyrimidine **16f** and gave the 2-pyrrolidino-guanidinopyridine **15f** in 80% yield. Reactions of piperidine and morpholine however, were slower and did not consume all the pyridopyrimidine even after 7 days, with the 4-piperidino-pyrido[2,3-*d*]pyrimidine **16g** being the most resistant. In these slow reactions we observed increased yields of the 2-aminopyridine **13** that indicated hydrolysis of the pyridopyrimidines or guanidines. Hydrolyses of pyrido[2,3-*d*]pyrimidines to 2-aminonicotinonitriles in the presence of a C-4 leaving group under basic conditions are known,[35] while in the absence of a leaving group hydrolysis can occur on treatment with a Grignard reagent after nucleophilic addition at the C-2 position and subsequent ring opening.[36] Similar hydrolyses of guanidines to the corresponding arylamines have also been reported either in basic[37] or acidic conditions.[38] These results suggested that the 2-dialkylaminoguanidinopyridines **15f-h** were derived from the 4-dialkylaminopyrido[2,3-*d*]pyrimidines **16f-h** and not from the starting dithiazole **14**.

2.2. Investigation of the origins of 2-aminoguanidinopyridines **15**

To the best of our knowledge, there are no reports of a pyrimidine fragmenting to give a 2-aminoguanidine, although hydrolytic cleavage of pyrimidines is well documented.[35] Nevertheless, the above observations tentatively suggested that the 2-dialkylamino-guanidinopyridines **15f-h** were derived from the 4-dialkylaminopyrido[2,3-*d*]pyrimidines **16f-h**. As such, the three 4-dialkylaminopyrido[2,3-*d*]pyrimidines **16f-h** were treated with excess of the corresponding dialkylamine, and as expected, gave the 2-dialkylamino-guanidinopyridines **15f-h** in 65-78% yields (Table 2).

Table 2. Reactions of pyrido[2,3-*d*]pyrimidines **16f-h** with excess cyclic secondary dialkylamines.

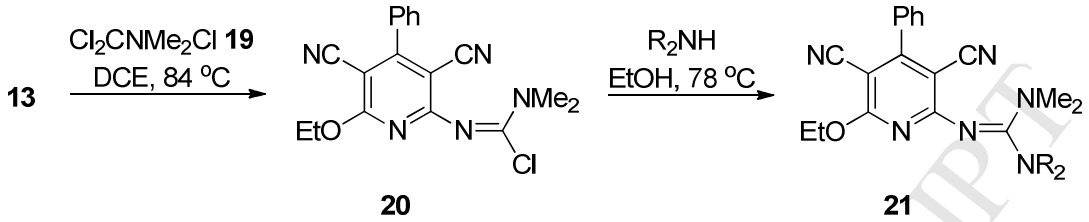


16f-h **15f-h**

Entry	R_2NH (equiv)	Solvent	Temp. (^oC)	Time	Yields (%)
1	pyrrolidine (20)	DCM	40	5 h	**15f** (65)
2	piperidine (20)	DCM	40	5 d	**16g** (87), **15g** (trace)
3	piperidine (40)	DCM	40	9 d	**16g** (43), **15g** (trace)
4	piperidine (40)	PhMe	110	6 h	**15g** (75)
5	morpholine (40)	DCM	40	6 d	-
6	morpholine (20)	PhMe	110	6 d	**15h** (78)

As above, the reaction times for the transformation of the 4-aminopyrido[2,3-*d*]pyrimidines **16f-h** correlated with the nucleophilicity of the secondary amines *i.e.* pyrrolidine > piperidine > morpholine. While pyrido[2,3-*d*]pyrimidine **16f** reacted fast with pyrrolidine (Table 2, entry 1) to give 2-pyrrolidinoguanidinopyridine **15f** in 65% yield, the respective reactions of piperidine and morpholine were slower in DCM at *ca.* 40 ^oC and required heating in PhMe at *ca.* 110 ^oC with a large excess of amine to consume fully the starting pyrido[2,3-*d*]pyrimidine

(Table 2, entries 4 and 6). Interestingly, similar 2-aminoguanidinopyridines **21** have been prepared from the 2-aminopyridine **13** and *N*,*N*-dichlorodimethyliminochloride (**19**), *via* the (*E*)-*N*,*N*-dimethylcarbamimidic chloride **20** (Scheme 7).[29a]



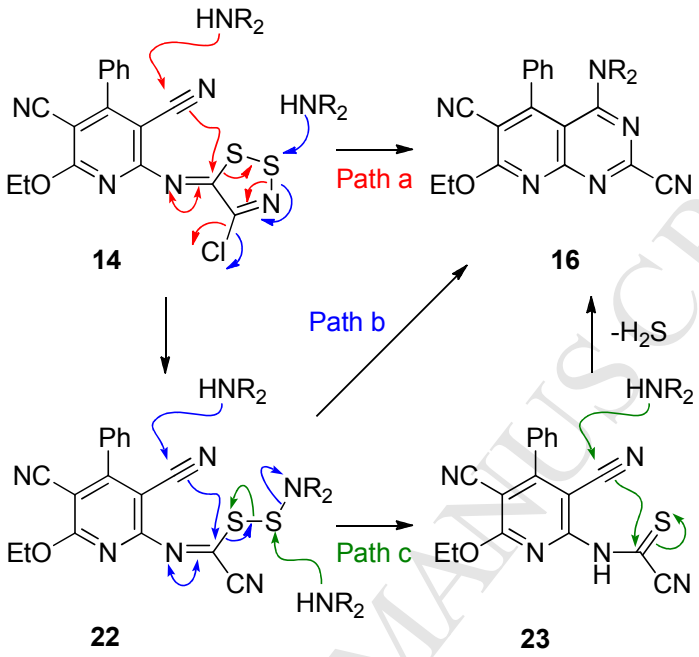
Scheme 7

2.3. Mechanistic Rationale for the Formation of Compounds **15-18**

The 4-dialkylaminopyrido[2,3-*d*]pyrimidines **16** can be obtained *via* two possible mechanistic pathways (path a and b, Scheme 8). The first (path a), involves a nucleophilic addition of the alkylamine to the cyano group at the pyridine C-3 position, followed by a subsequent attack of the newly formed amidine onto the dithiazole C-5 position causing fragmentation and elimination of S_2 and HCl. The second mechanistic pathway (path b) involves an ANRORC style nucleophilic attack of the alkylamine onto the S-2 position of the dithiazole ring leading to ring cleavage and formation of the disulfide intermediate **22**. A second alkylamine then attacks the cyano group at the pyridine C-3 position and the subsequent amidine cyclises onto the C-5 position of the dithiazole leading to elimination of S_2 and HCl.

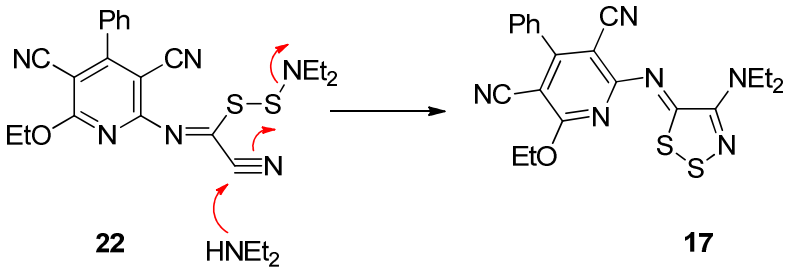
Moreover, since dithiazolylideneamines can be converted to cyanothioformamides upon treatment with a range of nucleophiles such as amines, hydroxide and triphenylphosphine,[15c] a reaction believed to occur *via* a ring opened disulfide intermediate like **22**,[15c] then the possibility that these can also be reaction intermediates must be considered. In fact, cyanothioformanilides bearing an *ortho*-cyano substituents readily cyclise in neat alcohols heated at reflux to form pyrimidines.[20a,b] The *in situ* conversion of the disulfide intermediates

22 into cyanothioformamides **23** and subsequent cyclisation of the latter to give 4-alkyl-aminopyrido[2,3-*d*]pyrimidines **16** (path c) is therefore plausible, however, under our reaction conditions we saw no trace of the proposed cyanothioformamides **23**.



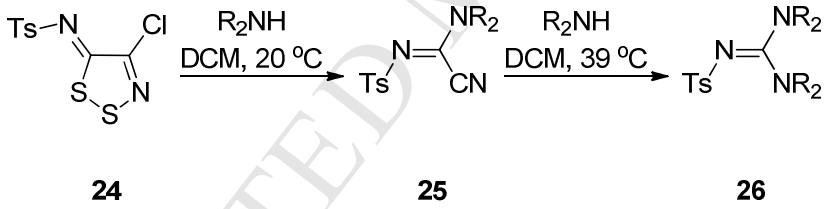
Scheme 8

There is insufficient experimental data to clarify which of the three mechanisms dominates, however, the formation of the 4-diethylaminodithiazole **17** provides some support for path b. Direct nucleophilic substitution of the dithiazole C-4 chlorine is known to be difficult,[8a] and Kim,[39] has provided strong evidence that 4-aminodithiazoles are formed *via* an ANRORC[40] style reaction whereby an amine initially cleaves the dithiazole to give a disulfide intermediate similar to structure **22** of path b, Scheme 8, and subsequent addition of another amine to the neigbouring carbonitrile affords an amidine that cyclizes onto the S-2 atom, eliminating the first amine and affording the dithiazolylidene **17** (Scheme 9).



Scheme 9

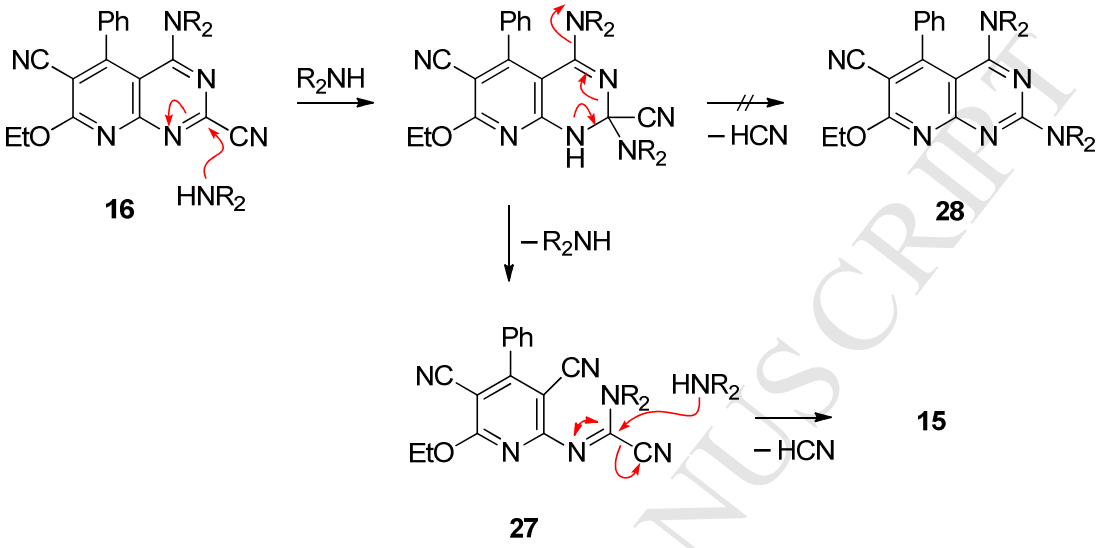
To the best of our knowledge, there is only one report on the transformation of a dithiazol-ylideneamine to a guanidine: (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylbenz-enesulfonamide (**24**) treated with secondary amines gave *N*-(diaminoalkylate)-4-methyl-benzenesulfonamides **26** in moderate to high yields (40-99%). The reaction rapidly gives the isolable (*Z*)-*N'*-tosylcarbamimidoyl cyanide **25** that on further treatment with dialkylamine converts to the guanidine **26** (Scheme 10).[41]



Scheme 10

In our reaction, however, the 2-aminoguanidinopyridines **15** form from the 4-aminopyrido-[2,3-*d*]pyrimidines **16**. Presumably, excess alkylamine attacks the electrophilic C-2 position of the pyrimidine, leading to ring opening and formation of the carbamidoyl cyanide **27**. Since this species was not observed in the reaction mixture, we must assume that it was sufficiently more electrophilic that the starting 4-aminopyrido[2,3-*d*]pyrimidine **16** and, as such, rapidly gets converted into the observed guanidines **15**. Worthy of note was that activated carbonitriles can undergo direct nucleophilic substitution[42] but no 2,4-bisalkyl-

aminopyrido[2,3-*d*]pyrimidines **28** were observed in the reaction mixtures, which being more electron rich than the starting carbonitriles **16** should have been comparatively stable and therefore, isolable.

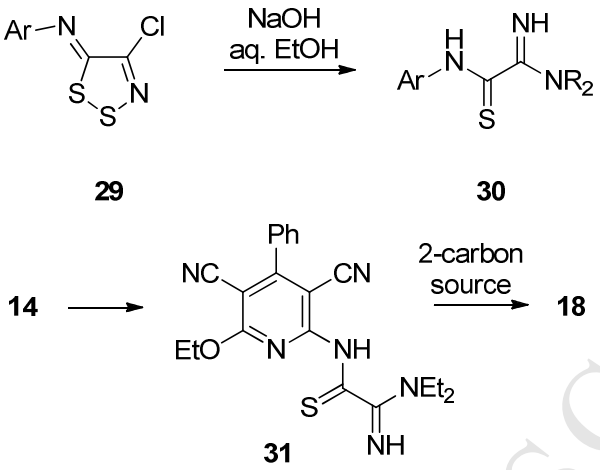


Scheme 11

Moreover, the carbamimidoyl cyanide intermediate **27** can also form by direct attack of the amine on the dithiazole C-5 position. Since we saw no trace of this carbamimidoyl cyanide during the reaction of the dithiazole **14** with the alkylamines, we tentatively consider this pathway to be less likely.

The origin of green compound **18** was intriguing and remains a puzzle. A review of the literature revealed that treatment of the dithiazolylidene **29** with NaOH in EtOH leads to ring opening of the dithiazole forming the reddish *N'*-arylthiocarbamoyl-*N*,*N*-dialkylamidine **30** in good to excellent yields (68-99%) (Scheme 12).[43] A similar fragmentation of the dithiazole **11** can lead to intermediate **31** which presumably can incorporate a 2-carbon source from an additional dithiazole molecule, or degradation product thereof, to give the observed quinoidal

2,2′-bithiazole **18**. This complex and intriguing transformation is now under further investigation and will be the subject of a future publication.



Scheme 12

3. Conclusions

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**14**) reacts with *n*-$BuNH_2$ and $BnNH_2$ to give the guanidines **15a** and **15b** in 32 and 82% yields, respectively. In contrast, treatment of the dithiazole **14** with Et_2NH, *n*-Pr_2NH or Bn_2NH gave the analogous 4-dialkylaminopyrido[2,3-*d*]pyrimidines **16c-e** in high yields, which on further treatment with dialkylamines can be converted into guanidines. The reactions of the dithiazole **14** are sometimes accompanied by minor side products (*e.g.*, the 4-diethylaminodithiazole **17** and the quinoidal-2,2′-bithiazole **18**) that indicate the presence of ANRORC style reaction mechanisms.

4. Experimental

4.1. General procedures

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}).[44] 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). Melting points were determined using a Wagner & Munz Polytherm A hot stage microscope apparatus. Solvents used for recrystallization are indicated after the melting point. UV/vis 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. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 (at 300 and 75 MHz, respectively), or a 500 machine (at 500 and 125 MHz, respectively). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. CH assignments were made based on DEPT 135 spectroscopy. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GCMS with direct inlet probe, while high resolution (EI) mass spectra were recorded on a VG Autospec "Q" instrument. MALDI TOF mass spectra were recorded on a Bruker Autoflex III Smartbeam instrument. 2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine (**14**),[27] was prepared according to the literature.

4.2. Reactions of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine (14) with primary amines (see Table 1)

4.2.1. 1,3-Di-n-*butyl-2-(3,5-dicyano-6-ethoxy-4-phenylpyridin-2-yl)guanidine* ***(15a)*** *(typical procedure).* To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine (**14**) (50.0 mg, 0.125 mmol) in DCM (2 mL) at *ca*. 20 ^{o}C and protected with $CaCl_2$ drying tube, was added *n*-$BuNH_2$ (54.8 μL, 0.520 mmol) and the mixture was heated at reflux for 4 h. On cooling to *ca.* 20 ^{o}C the reaction mixture was adsorbed onto silica and chromatography (*n*-hexane) gave S_8 (7.5 mg, 94%). Further elution (DCM/*t*-BuOMe, 9:1) gave the *title compound* **15a** (16.7 mg, 32%) as colourless needles, mp 204-205 ^{o}C (from EtOH); R_f 0.32 (DCM/*t*-BuOMe, 9:1); (found: C, 68.93; H, 7.38; N, 19.99. $C_{24}H_{30}N_6O$ requires C, 68.87; H, 7.22; N, 20.08%); λ_{max}(DCM)/nm 249 inf (log ε 3.25), 315 (3.61), 347 (3.55); ν_{max}/cm^{-1} 3337m (NH), 2222m (C≡N), 1599w, 1578m, 1526s, 1493s, 1464m, 1447w, 1423s, 1381w, 1335m, 1308w, 1271w, 1246w, 1231w, 1184m, 1148w, 1076w, 1013w, 934w, 912w, 822w, 785m; δ_H(500 MHz, $CDCl_3$) 7.53-7.49 (5H, m, Ph *H*), 4.37 (2H, q, *J* 7.1, C*H*$_2$O), 3.40 (4H, br s, C*H*$_2$), 1.68-1.62 (4H, m, C*H*$_2$), 1.49 (3H, t, *J* 7.3, C*H*$_3$), 1.46-1.42 (4H, m, C*H*$_2$), 1.30 (1H, d, *J* 6.6, N*H*), 1.25 (1H, s, N*H*), 0.97 (6H, t, *J* 7.3, C*H*$_3$); δ_C(125 MHz, $CDCl_3$) 164.8 (s), 160.3 (s), 156.1 (s), 134.1 (s), 130.3 (d), 128.7 (d), 128.6 (d), 116.3 (s), 115.2 (s), 94.2 (s), 93.6 (s), 93.3 (s), 63.5 (t), 41.7 (t), 31.6 (t), 20.1 (t), 14.4 (q), 13.7 (q); *m/z* (EI) 418 (M^+, 100%), 389 (46), 376 (37), 361 (25), 347 (39), 333 (25), 320 (33), 305 (35), 291 (14), 278 (17), 262 (44), 236 (45), 220 (43), 165 (31), 115 (18), 99 (15), 72 (34), 57 (19).

4.2.2. 1,3-Dibenzyl-2-(3,5-dicyano-6-ethoxy-4-phenylpyridin-2-yl)guanidine ***(15b)****.* Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxy-pyridine (**14**) (50.0 mg, 0.125 mmol) with $BnNH_2$ (56.9 μL, 0.520 mmol) heated at reflux for

7 h gave on chromatography (*n*-hexane) S_8 (7.8 mg, 98%) and on further elution (DCM) gave the *title compound* **15b** (49.9 mg, 82%) as colourless prisms, mp 230-231 ^oC (from EtOH); R_f 0.55 (DCM); λ_{max}(DCM)/nm 244 inf (log ε 3.38), 312 (3.58), 347 (3.56); ν_{max}/cm^{-1} 3335m (NH), 2222m (C≡N), 1599w, 1578m, 1530s, 1493s, 1466m, 1447w, 1423s, 1381w, 1337m, 1315w, 1269m, 1246w, 1231w, 1184m, 1148m, 1076w, 1014m, 910w, 822w, 785m; δ_H(500 MHz, $CDCl_3$) NH resonance missing 7.51-7.48 (10H, m, Ph *H*), 7.37 (5H, s, Ph *H*), 4.56 (4H, br s, C*H*$_2$Ph), 3.68 (2H, q, *J* 7.0, C*H*$_2$O), 1.11 (3H, t, *J* 7.0, C*H*$_3$); δ_C(125 MHz, $CDCl_3$) one C (d) and one C (s) resonance missing, 164.6 (s), 163.8 (s), 160.3 (s), 155.8 (s), 134.2 (s), 130.2 (br d), 129.0 (br d), 128.7 (d), 128.5 (d), 128.3 (d), 116.6 (s), 115.2 (s), 95.7 (s), 82.2 (s), 63.3 (t), 46.1 (t), 14.0 (q); *m/z* (EI) 486 (M^+, 3%), 414 (11), 395 (6), 385 (6), 344 (9), 316 (33), 288 (4), 220 (5), 165 (7), 106 (16), 91 (29), 70 (100), 55 (38); (found M^+, 486.2189 $C_{30}H_{26}N_6O$ requires *M*, 486.2168).

4.3. Reactions of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine (14) with secondary amines (see Table 1)

*4.3.1. 4-(Diethylamino)-7-ethoxy-5-phenylpyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile (**16c**) (typical procedure).* To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine (**14**) (50.0 mg, 0.125 mmol) in DCM (2 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, was added Et_2NH (53.6 μL, 0.520 mmol) and the mixture was heated at reflux. After 3.5 h TLC showed the presence of 5 main products and the reaction mixture was allowed to cool to *ca.* 20 ^oC, adsorbed onto silica and chromatography (*n*-hexane) gave S_8 (6.9 mg, 86%). Further elution (*n*-hexane/DCM, 1:1) gave the *title compound* **16c** (39.1 mg, 84%) as yellow prisms, mp 158-159 ^oC (from *c*-hexane/EtOH); R_f 0.16 (*n*-hexane/DCM, 1:1); (found: C, 67.87; H, 5.48; N, 22.51.

$C_{21}H_{20}N_6O$ requires C, 67.73; H, 5.41; N, 22.57%); λ_{max}(DCM)/nm 242 (log ε 3.08), 274 (3.08), 318 (2.96), 363 (3.24); ν_{max}/cm^{-1} 2997w, 2982w and 2941w (alkyl CH), 2220m (C≡N), 1589m, 1578m, 1531s, 1497m, 1485s, 1437w, 1422m, 1383m, 1371w, 1360m, 1344m, 1267m, 1213m, 1163m, 1076m, 1026w, 1001w, 918w, 853w, 804w, 787m, 752s, 733w, 706m; δ_H(300 MHz, $CDCl_3$) 7.54 (5H, s, Ph *H*), 4.64 (2H, q, *J* 7.1, C*H*$_2$O), 3.82-3.71 (4H, m, C*H*$_2$N), 1.48 (3H, t, *J* 7.1, C*H*$_3$), 1.40 (3H, t, *J* 7.2, C*H*$_3$), 1.32 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.1 (s), 161.4 (s), 160.7 (s), 135.3 (s), 133.3 (s), 130.6 (d), 128.8 (d), 128.5 (d), 115.3 (s), 114.2 (s), 108.9 (s), 96.1 (s), 91.3 (s), 65.1 (t), 46.2 (t), 44.2 (t), 14.44 (q), 14.37 (q), 11.8 (q); *m/z* (EI) 372 (M$^+$, 100%), 343 (59), 315 (30), 288 (30), 274 (13), 262 (10), 247 (8), 220 (20), 165 (46), 109 (72), 96 (21), 81 (29), 72 (28), 69 (13), 56 (22). Further elution (*n*-hexane/DCM, 1:4) gave 2-amino-6-ethoxy-4-phenylpyridine-3,5-dicarbo-nitrile (**13**) (2.0 mg, 6%) as colourless prisms, mp 238-239 ^{o}C (lit.,[29c] 233-234 ^{o}C) (from $CHCl_3$), identical to an authentic sample. Further elution (*n*-hexane/*t*-BuOMe, 7:3) gave *2-[4-(diethyl-amino)-5*H*-1,2,3-dithiazol-5-ylideneamino]-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile* (**17**) (2.7 mg, 5%) as red prisms, mp 174-175 ^{o}C (from *c*-hexane/EtOH); R_f 0.57 (*n*-hexane/*t*-BuOMe, 7:3); λ_{max}(DCM)/nm 286 (log ε 3.28), 401 inf (2.99), 452 inf (2.97), 497 (3.12), 531 (3.07); ν_{max}/cm^{-1} 3057w (Ar CH), 2980w and 2932w (alkyl CH), 2224m (C≡N), 1584w, 1547s, 1520m, 1497w, 1474s, 1454m, 1431s, 1412m, 1379m, 1335s, 1279w, 1267m, 1234m, 1198w, 1167m, 1103w, 1078w, 1063w, 1045w, 1024m, 982w, 949w, 934w, 922w, 907w, 841w, 814w, 789m, 773m, 748s, 729w, 706s; δ_H(300 MHz, $CDCl_3$) 7.57 (5H, s, Ph *H*), 4.81 (2H, q, *J* 7.1, C*H*$_2$O), 3.93 (4H, q, *J* 7.0, C*H*$_2$N), 1.59 (3H, t, *J* 7.1, C*H*$_3$), 1.27 (6H, t, *J* 7.0, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.6 (s), 162.1 (s), 160.9 (s), 160.3 (s), 160.0 (s), 133.1 (s), 130.9 (d), 129.0 (d), 128.7 (d), 115.1 (s), 114.1 (s), 99.0 (s), 91.9 (s), 66.8 (t), 45.9 (t), 14.6 (q), 13.7 (q); *m/z* (EI) 436 (M$^+$, 83%), 421 (18), 403 (49), 390 (9), 376 (47), 344 (12), 306 (9), 279 (12), 220 (15), 165 (25), 98 (47), 83 (74), 70 (100), 64 (12), 55 (31); (found M$^+$, 436.1144

$C_{21}H_{20}N_6OS_2$ requires *M*, 436.1140). Further elution (*t*-BuOMe) gave *6,6'-{(1*Z*,1'*Z*)-[(*E*)-4,4'-bis(diethylamino)-5*H*,5'*H*-(2,2'-bithiazolylidene)-5,5'-diylidene]bis(azanylylidene)}-bis-(2-ethoxy-4-phenylpyridine-3,5-dicarbonitrile)* (**18**) (2.2 mg, 2%) as green needles, mp > 300 ^{o}C (from DCE); R_f 0.68 (*t*-BuOMe); (found, C, 63.33; H, 4.80; N, 20.05. $C_{44}H_{40}N_{12}O_2S_2$ requires C, 63.44; H, 4.84; N, 20.18%); λ_{max}(DCM)/nm 252 (log ε 3.60), 324 (3.17), 444 (3.18), 625 inf (3.22), 678 (3.66), 742 (3.94); ν_{max}/cm^{-1} 2986w, 2938w and 2872w (aryl CH), 2228m (C≡N), 1543m, 1464s, 1441m, 1400m, 1352s, 1337m, 1325m, 1298m, 1263s, 1233m, 1165m, 1126m, 1080m, 1043m, 1015w, 891w, 843w, 816w, 797w, 772w, 748m, 708m, 698w, 644w, 633m; δ_H(300 MHz, $CDCl_3$) 7.59-7.58 (10H, m, Ph *H*), 4.90 (4H, q, *J* 7.5, C*H*$_2$O), 3.75 (6H, t, *J* 6.6, C*H*$_3$), 1.87-1.83 (8H, m, C*H*$_2$N), 1.40-1.32 (12H, m, C*H*$_3$); *m/z* (MALDI-TOF) 832 (M^+, 7%), 454 (100), 373 (37), 348 (12). ^{13}C NMR spectra could not be obtained due to insolubility.

4.3.2. 4-(Di-n-*propylamino)-7-ethoxy-5-phenylpyrido[2,3*-d*]pyrimidine-2,6-dicarbonitrile (**16d**).* Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine (**14**) (50.0 mg, 0.125 mmol) with *n*-Pr_2NH (71.1 μL, 0.520 mmol) gave the *title compound* **16d** (36.5 mg, 73%) as yellow prisms, mp 170-171 ^{o}C (from *c*-hexane/EtOH); R_f 0.28 (*n*-hexane/DCM, 1:1); (found: C, 68.93; H, 5.95; N, 20.91. $C_{23}H_{24}N_6O$ requires C, 68.98; H, 6.04; N, 20.99%); λ_{max}(DCM)/nm 243 (log ε 3.05), 265 inf (3.01), 275 (3.03), 319 (2.92), 365 (3.22); ν_{max}/cm^{-1} 2965w (alkyl CH), 2226m (C≡N), 1591m, 1578m, 1530s, 1497m, 1443m, 1429w, 1416w, 1371m, 1342m, 1267w, 1248m, 1207w, 1159m, 1103w, 1024w, 1013w, 980w, 922w, 868w, 802w, 787w, 727w; δ_H(300 MHz, $CDCl_3$) 7.54 (5H, s, Ph *H*), 4.65-4.62 (2H, m, C*H*$_2$O), 3.71-3.62 (4H, m, C*H*$_2$N), 1.81-1.76 (4H, m, C*H*$_2$), 1.48 (3H, t, *J* 6.7, C*H*$_3$), 1.05-0.95 (6H, m, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.1 (s), 161.3 (s), 160.7 (s), 135.8 (s), 133.3 (s), 130.6 (d), 128.8 (d), 128.5 (d), 115.3 (s),

114.3 (s), 109.1 (s), 96.2 (s), 91.2 (s), 65.1 (t), 53.2 (t), 51.2 (t), 22.4 (t), 20.0 (t), 14.4 (q), 11.3 (q), 11.0 (q); *m/z* (EI) 400 (M^+, 15%), 371 (8), 357 (14), 315 (9), 272 (7), 220 (8), 165 (29), 137 (16), 124 (60), 56 (13).

*4.3.3. 4-(Dibenzylamino)-7-ethoxy-5-phenylpyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile (**16e**).* Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine (**14**) (50.0 mg, 0.125 mmol) with Bn_2NH (526 μL, 2.60 mmol) gave the *title compound* **16e** (31.0 mg, 50%) as yellow needles, mp 185-186 ^oC (from EtOH); R_f 0.32 (*n*-hexane/DCM, 1:1); (found C, 75.19; H, 4.98; N, 17.04. $C_{31}H_{24}N_6O$ requires C, 74.98; H, 4.87; N, 16.92%); λ_{max}(DCM)/nm 247 (log ε 3.44), 271 (3.46), 315 (3.27), 364 (3.59), 386 inf (3.40); ν_{max}/cm^{-1} 3063w and 3034w (Ar CH), 2994w, 2982w and 2940w (alkyl CH), 2226m (C≡N), 1593m, 1578m, 1530s, 1497w, 1445m, 1429m, 1381m, 1366m, 1340m, 1267w, 1233m, 1180m, 1157w, 1121w, 1082w, 1020w, 943m, 934w, 918w, 910w, 885w, 827w; δ_H(300 MHz, $CDCl_3$) 7.64-7.31 (15H, m, Ph *H*), 4.90 (4H, s, PhCH_2), 4.70 (2H, q, *J* 7.1, CH_2O), 1.52 (3H, t, *J* 7.1, CH_3); δ_C(75 MHz, $CDCl_3$) one C (d) resonance missing, 165.2 (s), 161.2 (s), 160.9 (s), 136.8 (s), 134.3 (s), 133.8 (s), 133.2 (s), 130.8 (d), 129.3 (d), 129.0 (d), 128.90 (d), 128.87 (d), 128.6 (d), 128.5 (d), 127.8 (d), 115.3 (s), 114.1 (s), 109.3 (s), 96.5 (s), 92.1 (s), 65.4 (t), 53.2 (t), 50.4 (t), 14.4 (q); *m/z* (EI) 496 (M^+, 10%), 405 (100), 377 (43), 350 (24), 325 (8), 165 (12), 91 (90), 84 (12), 65 (12).

*4.3.4. 7-Ethoxy-5-phenyl-4-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile (**16f**).* To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine (**14**) (50.0 mg, 0.125 mmol) in DCM (2 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, was added pyrrolidine (41.7 μL, 0.500 mmol) and the mixture was heated at reflux. After 10 min TLC showed the presence of 4 main products. The reaction mixture was allowed to cool to *ca.* 20 ^oC, adsorbed onto silica and chromatography

(*n*-hexane) gave S_8 (7.6 mg, 95%). Further elution (*n*-hexane/DCM, 1:1) gave the *title compound* **16f** (36.1 mg, 78%) as greenish-yellow needles, mp 217-218 ^{o}C (from EtOH); R_f 0.46 (*n*-hexane/DCM, 1:4); (found C, 67.91; H, 4.79; N, 22.46. $C_{21}H_{18}N_6O$ requires C, 68.09; H, 4.90; N, 22.69%); λ_{max}(DCM)/nm 242 (log ε 3.24), 274 (3.26), 318 (3.14), 365 (3.45); ν_{max}/cm^{-1} 3063w (Ar CH), 2997w, 2984w and 2870w (alkyl CH), 2226m (C≡N), 1591s, 1578m, 1530s, 1499w, 1474m, 1445m, 1412m, 1379m, 1362m, 1343w, 1327s, 1269m, 1236w, 1227w, 1194w, 1179w, 1155w, 1078w, 1018w, 989w, 961w, 914w, 881w, 853w, 791w; δ_H(300 MHz, $CDCl_3$) 7.54 (5H, s, Ph *H*), 4.63 (2H, q, *J* 7.1, C*H*$_2$O), 3.93 (2H, t, *J* 6.3, C*H*$_2$N), 3.80 (2H, t, *J* 6.9, C*H*$_2$N), 2.14-2.05 (4H, m, C*H*$_2$), 1.48 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.1 (s), 161.2 (s), 160.8 (s), 133.8 (s), 133.3 (s), 130.6 (d), 128.8 (d), 128.5 (d), 115.4 (s), 114.3 (s), 110.0 (s), 96.0 (s), 91.2 (s), 65.2 (t), 50.1 (t), 49.5 (t), 25.2 (t), 24.4 (t), 14.4 (q); *m/z* (EI) 370 (M$^+$, 48%), 341 (36), 313 (14), 272 (12), 220 (6), 193 (7) 165 (32), 138 (9), 122 (11), 95 (12), 79 (20), 70 (100), 55 (27). Further elution (*n*-hexane/DCM, 3:7) gave 2-amino-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**13**) (2.0 mg, 6%) as colourless prisms, mp 238-239 ^{o}C (lit.,[29c] 233-234 ^{o}C) (from $CHCl_3$), identical to an authentic sample. A final elution (DCM/*t*-BuOMe, 9:1) gave *2-(dipyrrolidin-1-ylmethyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile* (**15f**) (7.3 mg, 14%) as colourless prisms, mp 216-217 ^{o}C (from EtOH); R_f 0.68 (DCM/*t*-BuOMe, 9:1); λ_{max}(DCM)/nm 243 inf (log ε 3.36), 308 (3.57), 348 (3.24); ν_{max}/cm^{-1} 2980w, 2955w and 2880w (alkyl CH), 2212m (C≡N), 1585m, 1566m, 1510s, 1474m, 1441s, 1422w, 1398m, 1377m, 1360m, 1331s, 1277m, 1236w, 1215w, 1184w, 1169w, 1149w, 1090w, 1024m, 968w, 934w, 920w, 887w, 876w, 862w, 841w, 808w, 779m, 766m; δ_H(300 MHz, $CDCl_3$) 7.52-7.43 (5H, m, Ph *H*), 4.30 (2H, q, *J* 7.1, C*H*$_2$O), 3.47 (8H, br s, C*H*$_2$N), 1.90 (8H, br s, C*H*$_2$), 1.35 (3H, t, *J* 7.0, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.5 (s), 161.9 (s), 161.7 (s), 160.4 (s), 134.7 (s), 129.7 (d), 128.42 (d), 128.38 (d), 118.1 (s), 116.6 (s), 88.5 (s), 81.1 (s), 62.3 (t), 49.5 (t), 25.3 (t), 14.4 (q); *m/z* (EI) 414 (M$^+$,

12%), 400 (6), 386 (16), 357 (12), 344 (11), 316 (37), 288 (10), 274 (7), 220 (14), 165 (38), 139 (12), 124 (48), 98 (9), 85 (9), 70 (100), 55 (36); (found M^+, 414.2184 $C_{24}H_{26}N_6O$ requires *M*, 414.2168).

*4.3.5. 7-Ethoxy-5-phenyl-4-(piperidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile* (**16g**). Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine (**14**) (50.0 mg, 0.125 mmol) with piperidine (49.4 μL, 0.500 mmol) gave S_8 (7.5 mg, 94%). Further elution (*n*-hexane/DCM, 1:4) gave the *title compound* **16g** (35.6 mg, 74%) as yellow needles, mp 190-191 ^{o}C (from EtOH); R_f 0.54 (*n*-hexane/DCM, 1:4); (found C, 68.95; H, 5.06; N, 21.78. $C_{22}H_{20}N_6O$ requires C, 68.73; H, 5.24; N, 21.86%); λ_{max}(DCM)/nm 246 (log ε 3.33), 277 (3.33), 317 (3.23), 363 (3.51), 386 inf (3.32); ν_{max}/cm^{-1} 3066w (Ar CH), 2996w, 2949w, 2921w and 2870w (alkyl CH), 2224m (C≡N), 1587m, 1576m, 1529s, 1518s, 1504w, 1474m, 1443m, 1412m, 1366m, 1342m, 1287w, 1258m, 1236m, 1229m, 1161w, 1136w, 1111w, 1074w, 1018m, 953w, 932w, 916w, 879w, 851w, 831w, 788w; δ_H(500 MHz, $CDCl_3$) 7.54 (5H, s, Ph *H*), 4.66 (2H, q, *J* 7.1, C*H*$_2$O), 3.98-3.90 (4H, m, C*H*$_2$N), 1.83-1.74 (6H, m, C*H*$_2$), 1.48 (3H, t, *J* 7.1, C*H*$_3$); δ_C(125 MHz, $CDCl_3$) 165.1 (s), 161.5 (s), 160.8 (s), 135.2 (s), 133.4 (s), 130.7 (d), 128.9 (d), 128.6 (d), 115.3 (s), 114.3 (s), 108.8 (s), 96.1 (s), 91.4 (s), 65.2 (t), 50.2 (t), 46.7 (t), 26.7 (t), 25.1 (t), 24.0 (t), 14.4 (q); *m/z* (EI) 384 (M^+, 33%), 355 (31), 316 (6), 300 (5), 288 (5), 276 (9), 248 (18), 220 (8), 192 (5), 165 (37), 136 (12), 121 (13), 109 (14), 84 (50), 70 (29), 55 (62). Further elution (*n*-hexane/DCM, 1:4) gave 2-amino-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**13**) (3.3 mg, 10%) as colourless prisms, mp 238-239 ^{o}C (lit.,[29c] 233-234 ^{o}C) (from $CHCl_3$), identical to an authentic sample. A final elution (DCM/*t*-BuOMe, 9:1) gave *2-(dipiperidin-1-ylmethylene-amino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile* (**15g**) (6.1 mg, 11%) as colourless needles, mp 186-187 ^{o}C (from EtOH); R_f 0.78 (DCM/*t*-BuOMe, 9:1); (found C, 70.62; H,

6.90; N, 19.06. $C_{26}H_{30}N_6O$ requires C, 70.56; H, 6.83; N, 18.99%); λ_{max}(DCM)/nm 245 (log ε 3.19), 314 (3.40), 341 (3.29); ν_{max}/cm^{-1} 2978w, 2945w, 2924w and 2857w (alkyl CH), 2214m (C≡N), 1582w, 1564w, 1533m, 1512m, 1483s, 1476s, 1437s, 1408m, 1381m, 1331m, 1317s, 1267m, 1258m, 1225m, 1190m, 1153m, 1140w, 1105w, 1082w, 1072w, 1022m, 982w, 955w, 920w, 878w, 860w, 804w, 779m, 765m; δ_H(300 MHz, $CDCl_3$) 7.54-7.46 (5H, m, Ph *H*), 4.42 (2H, q, *J* 7.1, C*H*$_2$O), 3.25 (8H, s, C*H*$_2$N), 1.61 (12H, s, C*H*$_2$), 1.41 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) one C (s) and one C (t) resonance missing, 165.6 (s), 164.1 (s), 160.5 (s), 134.2 (s), 130.1 (d), 128.6 (d), 128.5 (d), 117.3 (s), 115.7 (s), 91.6 (s), 84.7 (s), 63.1 (t), 49.8 (t), 26.8 (t), 25.1 (t), 24.3 (t), 14.4 (q); *m/z* (EI) 442 (M^+, 8%), 359 (12), 330 (28), 220 (5), 165 (7), 84 (100), 69 (14), 56 (21).

*4.3.6. 7-Ethoxy-5-phenyl-4-(morpholin-4-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile (**16h**).* Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine (**14**) (50.0 mg, 0.125 mmol) with morpholine (43.7 μL, 0.500 mmol) gave gave S_8 (7.1 mg, 89%). Further elution (*n*-hexane/DCM, 1:4) gave the *title compound* **16h** (37.2 mg, 77%) as an orange powder, mp 165-166 ^oC (from EtOH); R_f 0.17 (*n*-hexane/DCM, 1:4); λ_{max}(DCM)/nm 244 (log ε 3.37), 275 (3.39), 319 (3.23), 364 (3.53), 385 inf (3.34); ν_{max}/cm^{-1} 3067w (Ar CH), 2963w and 2845w (alkyl CH), 2226m (C≡N), 1626w, 1589m, 1578m, 1530s, 1520s, 1474m, 1439m, 1412m, 1381m, 1368m, 1356w, 1344m, 1298w, 1275w, 1250s, 1238w, 1196w, 1157w, 1119m, 1040w, 1016w, 962m, 916m, 885m, 843w, 799w; δ_H(300 MHz, $CDCl_3$) 7.55 (5H, s, Ph *H*), 4.65 (2H, q, *J* 7.1, C*H*$_2$O), 4.03 (2H, t, *J* 4.8, C*H*$_2$O), 3.95 (2H, t, *J* 4.2, C*H*$_2$O), 3.87 (2H, t, *J* 4.7, C*H*$_2$N), 3.82 (2H, t, *J* 4.8, C*H*$_2$N), 1.49 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.1 (s), 160.9 (s), 160.8 (s), 135.4 (s), 133.2 (s), 130.8 (d), 128.9 (d), 128.6 (d), 115.1 (s), 114.0 (s), 108.5 (s), 96.5 (s), 92.3 (s), 66.5 (t), 65.9 (t), 65.4 (t), 48.9 (t), 45.8 (t), 14.4 (q); *m/z* (EI) 386 (M^+, 100%), 357 (54), 330 (8),

300 (11), 288 (14), 274 (15), 272 (16), 261 (9), 248 (14), 220 (17), 193 (11), 165 (60), 138 (17), 124 (13), 85 (45), 77 (12), 66 (28), 56 (16); (found: M^+, 386.1482 $C_{21}H_{18}N_6O_2$ requires *M*, 386.1491). Further elution (*n*-hexane/DCM, 1:4) gave 2-amino-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**13**) (4.0 mg, 12%) as colourless prisms, mp 238-239 °C (lit.,[29c] 233-234 °C) (from $CHCl_3$), identical to an authentic sample. A final elution (DCM/*t*-BuOMe, 4:1) gave *2-(dimorpholinomethylene-amino)-6-ethoxy-4-phenylpyridine-3,5-di-carbonitrile* (**15h**) (1.1 mg, 2%) as colourless prisms, mp 227-229 °C (from EtOH); R_f 0.55 (DCM/*t*-BuOMe, 4:1); (found: C, 64.47; H, 5.84; N, 18.89. $C_{24}H_{26}N_6O_3$ requires C, 64.56; H, 5.87; N, 18.82%); λ_{max}(DCM)/nm 241 (log ε 3.43), 312 (3.55), 338 (3.51); ν_{max}/cm^{-1} 2970w, 2914w, 2893w and 2855w (alkyl CH), 2218m (C≡N), 1585w, 1570w, 1510w, 1483s, 1452w, 1439s, 1412m, 1369m, 1337w, 1317m, 1296w, 1265m, 1213w, 1193w, 1179m, 1155m, 1111s, 1092m, 1067w, 1036m, 1022m, 989m, 907w, 878m, 849w, 831w; δ_H(300 MHz, $CDCl_3$) 7.51 (5H, br s, Ph *H*), 4.46 (2H, q, *J* 7.1, CH_2O), 3.72 (8H, t, *J* 4.6, CH_2O), 3.33 (8H, t, *J* 4.6, CH_2N), 1.44 (3H, t, *J* 7.1, CH_3); δ_C(75 MHz, $CDCl_3$) 165.8 (s), 165.2 (s), 162.2 (s), 160.7 (s), 133.8 (s), 130.4 (d), 128.7 (d), 128.5 (d), 116.7 (s), 115.0 (s), 92.5 (s), 86.8 (s), 66.2 (t), 63.6 (t), 49.0 (t), 14.4 (q); *m/z* (EI) 446 (M^+, 18%), 360 (10), 332 (55), 303 (14), 288 (11), 275 (19), 220 (13), 165 (29), 112 (13), 86 (100), 69 (28), 56 (54).

4.4. Reactions of 4-dilakylaminopyrido[2,3-*d*]pyrimidine-2,6-dicarbonitriles 16f-h with excess dilakylamines (see Table 2)

*4.4.1. Reaction of 7-ethoxy-5-phenyl-4-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-di-carbonitrile (**16f**) with excess pyrrolidine (typical procedure).* To a stirred solution of 7-ethoxy-5-phenyl-4-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile (**16f**) (30.0 mg, 0.080 mmol) in DCM (2 mL) at *ca.* 20 °C and protected with $CaCl_2$ drying tube, was

added pyrrolidine (131 μL, 1.60 mmol) and the mixture was heated at reflux for 5 h until no starting materials remained (TLC). The reaction mixture was allowed to cool to *ca.* 20 ^{o}C, adsorbed onto silica and chromatography (DCM/*t*-BuOMe, 9:1) gave 2-(dipyrrolidin-1-yl-methyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**15f**) (21.5 mg, 65%) as colourless prisms, mp 216-217 ^{o}C (from EtOH) identical to that described above.

*4.4.2. Reaction of 7-ethoxy-5-phenyl-4-(piperidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-di-carbonitrile (**16g**) with excess piperidine.* Similar treatment of 7-ethoxy-5-phenyl-4-(piperidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile (**16g**) (30.7 mg, 0.080 mmol) with piperidine (316 μL, 3.20 mmol) in PhMe at reflux gave 2-(dipiperidin-1-ylmethyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**15g**) (7.4 mg, 21%) as colourless needles, mp 186-187 ^{o}C (from EtOH) identical to that described above.

*4.4.3. Reaction of 7-ethoxy-5-phenyl-4-(morpholin-4-yl)pyrido[2,3-*d*]pyrimidine-2,6-di-carbonitrile (**16h**) with excess morpholine.* Similar treatment of 7-ethoxy-5-phenyl-4-(morpholin-4-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile (**16h**) (30.7 mg, 0.080 mmol) with morpholine (138 μL, 1.60 mmol) gave 2-(dimorpholin-1-yl-methyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile (**15h**) (27.8 mg, 78%) as colourless prisms, mp 227-229 ^{o}C (from EtOH) identical to that described above.

4.5. X-ray crystallographic studies

Crystals of the quinoidal 2,2'-bithiazole **18** were grown by slow cooling of a hot 1,2-dichloroethane (DCE) solution. Data was collected using an Oxford Diffraction Xcalibur 3 diffractometer, and the structure was refined on the basis of F^2 using the SHELXTL and SHELX-97 program systems.[45]

*4.5.1. Crystal refinement data for compound **18**:* $C_{44}H_{40}N_{12}O_2S_2$, M = 833.00, monoclinic, $P2_1/n$ (no. 14), a = 14.2408(4), b = 21.0339(5), c = 14.7485(4) Å, β = 110.835(3)°, V = 4128.9(2) Å^3, Z = 4, D_c = 1.340 g cm^{-3}, μ(Cu-Kα) = 0.184 mm^{-1}, T = 173 K, dark green blocks; 14256 independent measured reflections (R_{int} = 0.0325), F^2 refinement,[45] R_1(obs) = 0.0588, wR_2(all) = 0.1805, 9072 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 65°], 541 parameters. CCDC deposition number 1036126.

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Graphical Abstract