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The conversion of 2-cyano cyanothioformanilides into 3-aminoindole-2-carbonitriles using triphenylphosphine

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ABSTRACT

2-Cyano cyanothioformanilide **3a** reacts with triphenylphosphine in the presence of water to give 2-(cyanomethyleneamino)benzonitrile **4a**, 2-(cyanomethylamino)benzonitrile **5**, 3-aminoindole-2-carbonitrile **2a** and (2-cyanoindol-3-yl)iminotriphenylphosphorane **6a**. In the presence of *p*-toluenesulfonic acid in MeOH the reaction between 2-cyano cyanothioformanilide **3a** and triphenylphosphine (2 equiv) gives 3-aminoindole-2-carbonitrile **2a** in 90% yield. Under the same conditions 2-(cyanomethyleneamino)benzonitrile **4a** gives anthranilonitrile **8a**, 3-aminoindole-2-carbonitrile **2a** and *N*-(2-cyanophenyl) formamide **9**. In addition, substituted 2-cyano cyanothioformanilides **3b**–**f** react with triphenylphosphine and *p*-toluenesulfonic acid in MeOH to give 3-aminoindole-2-carbonitriles **2b**–**f** in 63–75% yields. Under analogous conditions 2-cyano-4,5-dimethoxyphenyl cyanothioformanilide **2g** gives only 4,5-dimethoxyanthranilonitrile **8g** and 4,6,7-trimethoxyquinazoline-2-carbonitrile **14g**, but in refluxing dry PhMe in the absence of *p*-toluenesulfonic acid 2-cyano-4,5-dimethoxyphenyl cyanothioformanilide **3g**, (2-cyano-5,6-dimethoxyindol-3-yl)iminotriphenylphosphorane **6g** and 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **4g** are obtained. The structure of 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **4g** is supported unambiguously via independent synthesis and comparison to the isomeric 6,7-dimethoxyquinazoline-2-carbonitrile **15**. All new compounds are fully characterised and a tentative mechanism for the transformation of 2-cyano cyanothioformanilides to indoles is proposed.

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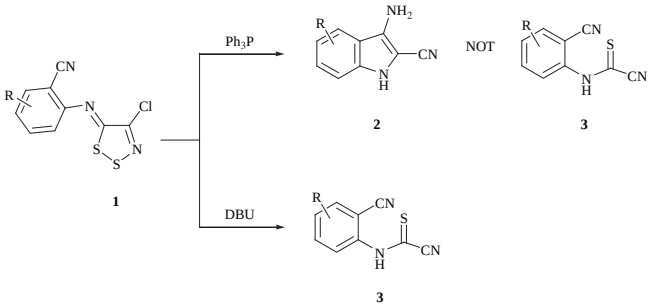
1. Introduction

Cyanothioformanilides (thiooxanilonitriles) demonstrate herbicidal activity,[1] and have been used extensively for the preparation of various heterocycles including pyrroles,[2a,b] imidazoles,[3a–k] oxazoles,[4a–c] 1,3,4-thiadiazoles,[5] quinazolines[6a–c] and other fused heterocycles.[7a–g] Furthermore, cyanothioformanilides participate in Diels–Alder[8a–c] and ene[9] reactions, can be N aroylated[10] and on addition to the nitrile of H_2O, H_2S or NH_2OH afford amino-oxothioacetylanilines, aminothioxothioacetylanilines (*N*-aryldithioxamides)[3d,11] or amidinothioformylanilines,[4c,12] respectively.

Cyanothioformanilides are traditionally prepared by the reaction of *N*-aryl isothiocyanates with cyanide,[3j,4c,6a,7f,7g,8c,13a–d] or bis(dialkylamino)acetonitriles[14] and also via dethiohydration of *N*-aryldithiooxamides,[13d,15] thionation-dethiohydration of *N*-arylthiooxalamides[15] and thionation–dehydration of aryloxalamides.[15] More recent methods involve treating 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzenes with either the oxidising agent *m*-CPBA,[16] the reducing agent $NaBH_3CN$,[17] or with nucleophilic (thiophilic) reagents such as aq NaOH,[18] NH_2OH,[19] *tert*-butylamine,[20] tryptamine,[21] *o*-aminophenethylamine and *o*-phenylenediamine,[22] triphenylphosphoraneylidenes,[23] triphenylphosphine in moist DCM[24a–h] and with the use of ethylmagnesium bromide (1 equiv).[24h,25]

Recently, we showed that treating 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino) benzonitriles **1** with triphenylphosphine (4 equiv) gave 3-aminoindole-2-carbonitriles **2** and not the expected 2-cyano cyanothioformanilides **3**.[26] The latter compounds could however, be prepared from the dithiazolimines **1** on treatment with DBU in high yield[27] (Scheme 1).



Scheme 1.

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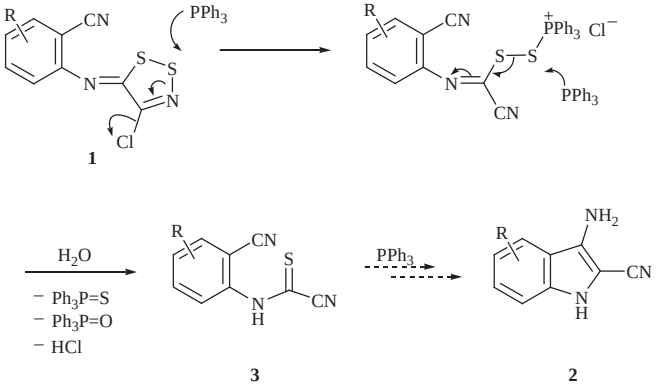
While a mechanism was not put forward for the formation of the indoles **2**, our initial thoughts focused on the triphenylphosphine behaving as a typical thiophile and attacking the dithiazolimine S-2 ring sulfur (Scheme 2). This would be expected to lead to the 2-cyano cyanothioformanilide **3**, however, as mentioned above this was not an observed.



Scheme 2.

In light of this a pure sample of 2-cyano cyanothioformanilide **3a** (R=H) was treated with triphenylphosphine to determine whether it was a possible intermediate in the dithiazole to indole conversion. Below we report our findings related to the treatment of 2-cyano cyanothioformanilides **3** with triphenylphosphine.

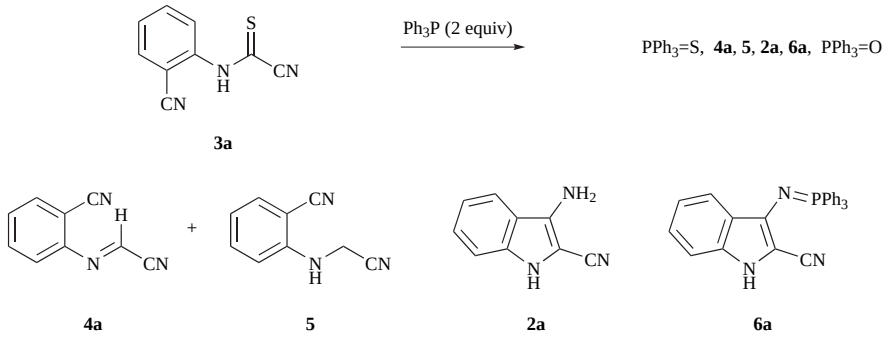
2. Results and discussion

2.1. Reaction of 2-cyano cyanothioformanilides with triphenylphosphine

Treatment of a solution of the cyanothioformanilide **3a** in dry DCM at ca. 20 °C with triphenylphosphine (2 equiv) rapidly gave several products: Triphenylphosphine sulfide, 2-(cyanomethylamino)benzonitrile **5**, the iminophosphorane **6a** and triphenylphosphine oxide (Table 1). Interestingly 3-aminoindole-2-carbonitrile **2a** was not observed, however, as the equivalents of water added to the reaction mixture were increased the yield of iminophosphorane **6a** decreased while that of the 3-aminoindole **2a** increased. The overall yields of indoles (**2a**+**6a**) remained relatively steady. Furthermore, a new compound **4a** was isolated in low yield, which was relatively unstable and identified as 2-(cyanomethyleneamino)benzonitrile **4a**.

2-(Cyanomethyleneamino)benzonitrile **4a** was obtained as colourless cotton fibres, mp 75–76 °C (from cyclohexane). Microanalysis and mass spectrometry supported the formula $C_9H_5N_3$ [*m*/*z* 155 (M^+, 28%)]. The presence of a cyano group was supported by an IR band at 2234 cm^{-1} and stretching frequencies could not be observed for any 1° or 2° amino functionality. The ^{13}C NMR spectrum showed nine separate carbon resonances of which four were quaternary carbons (DEPT-135 studies). Two of the quaternary signals (δ_C 118.3 and 116.2 ppm) were typical of cyano carbons, tentatively supporting the presence of two nitrile groups. The ^1H NMR spectrum identified five resonances, four of which clearly belonged to aromatic hydrogens (7.78, 7.68, 7.50 and 7.18 ppm) of a 1,2-disubstituted benzene ring. The signal at δ_H 7.63 ppm, however, was observed as a singlet. Based on the above data two possible structures could be proposed, which maintained the carbon and nitrogen connectivity of the starting 2-cyano

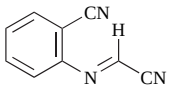
Table 1
Reaction of cyanothioformanilide **3a** (0.27 mmol) with triphenylphosphine (2 equiv) under a $CaCl_2$ drying tube



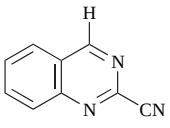
H_2O (equiv)	Solvent	Temp (°C)	Time (min)	Yields (%)					
				PPh_3=S	**4a**	**5**	**2a**	**6a**	PPh_3=O
0	DCM	20	5	78	—	20	—	70	54
1	DCM	20	3	80	—	25	6	63	58
2	DCM	20	1	80	7	30	13	50	70
3	DCM	20	1	80	6	25	21	48	71
0	PhH	20	5	84	11	38	3	45	69
0	PhH	40	5	78	5	23	1	69	49
0	PhH	80	1	87	6	traces	9	79	34
0	PhMe	20	3	86	6	17	5	68	51
0	PhMe[a]	20	10	79	—	28	58	7	80
0	PhMe	110	1	86	3	5	7	81	32
0	MeOH	20	70	45	9	63	—	23	49
0	MeOH[b]	20	60	69	4	59	5	23	71
0	MeOH[a]	20	50	72	—	9	90	—	80
0	MeOH	60	5	52	5	61	1	27	51

[a] PTSA (1 equiv) was added to the reaction mixture.
[b] PTSA (5 mol %) was added to the reaction mixture.

cyanothioformanilide **3a**; the 2-(cyanomethyleneamino)benzonitrile **4a** or the quinazoline-2-carbonitrile **7**. Fortunately, the latter compound **7** is known [mp 162–164 °C, ^{1}H NMR ($CDCl_3$) $\delta_{H\text{-}4}$ 9.55 ppm] and had been prepared via an unambiguous route starting from 2-chloroquinazoline.[28]

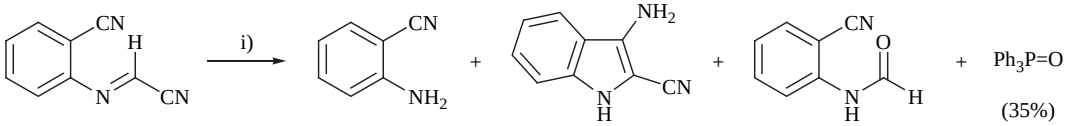


4a



7

When dry benzene or toluene was used as solvents, increasing the reaction temperature significantly raised the yield of the iminophosphorane **6a** to 79 and 81%, respectively, and gave total indole recoveries (**2a**+**6a**) approaching 90%. In the presence of *p*-toluenesulfonic acid (PTSA) (1 equiv) the reaction in toluene at ca. 20 °C gave mainly 3-aminoindole-2-carbonitrile **2a** rather than the iminophosphorane **6a**. It was rationalised that the use of a protic solvent such as methanol could lead to the formation of lesser amounts of indole products and greater amounts of the cyanomethylene **5** and this was indeed the case, although some indole products were still obtained. In this case, the addition of a catalytic quantity of PTSA (5 mol %) made little difference to the product distribution, however the addition of PTSA (1 equiv) gave rather surprisingly 3-aminoindole-2-carbonitrile **2a** in 90% yield. To better understand this result pure samples of compounds **4a**, **5** and **6a** were dissolved in methanol and treated with Ph_3P (2 equiv) and PTSA (1 equiv) at ca. 20 °C, respectively. After 24 h reaction, compounds **5** and **6a** proved to be stable. Compound **4a**, however, was consumed after 5 h and chromatography gave unreacted triphenylphosphine (59%), anthranilonitrile **8a** (14%), 3-aminoindole-2-carbonitrile **2a** (30%), *N*-(2-cyanophenyl)formamide **9** (53%) and triphenylphosphine oxide (35%) (Scheme 3).



4a **8a** (14%) **2a** (30%) **9** (53%)

Scheme 3. Reagents and conditions: (i) Ph_3P (2 equiv), PTSA (1 equiv) in MeOH at rt, 5 h.

The identity of the latter compound *N*-(2-cyanophenyl)formamide **9** was confirmed via an independent synthesis from anthranilonitrile **8a**, formic acid and zinc oxide according to a known procedure.[29] When the reaction was performed in the absence of triphenylphosphine, only anthranilonitrile **8a** and *N*-(2-cyanophenyl)formamide **9** were obtained. This unexpected transformation of the imine **4a** into the indole **2a** requires a formal reduction, and this could have been mediated by the triphenylphosphine. This transformation is now under further study.

2.2. Tentative mechanistic rational for the formation of compounds 2–6

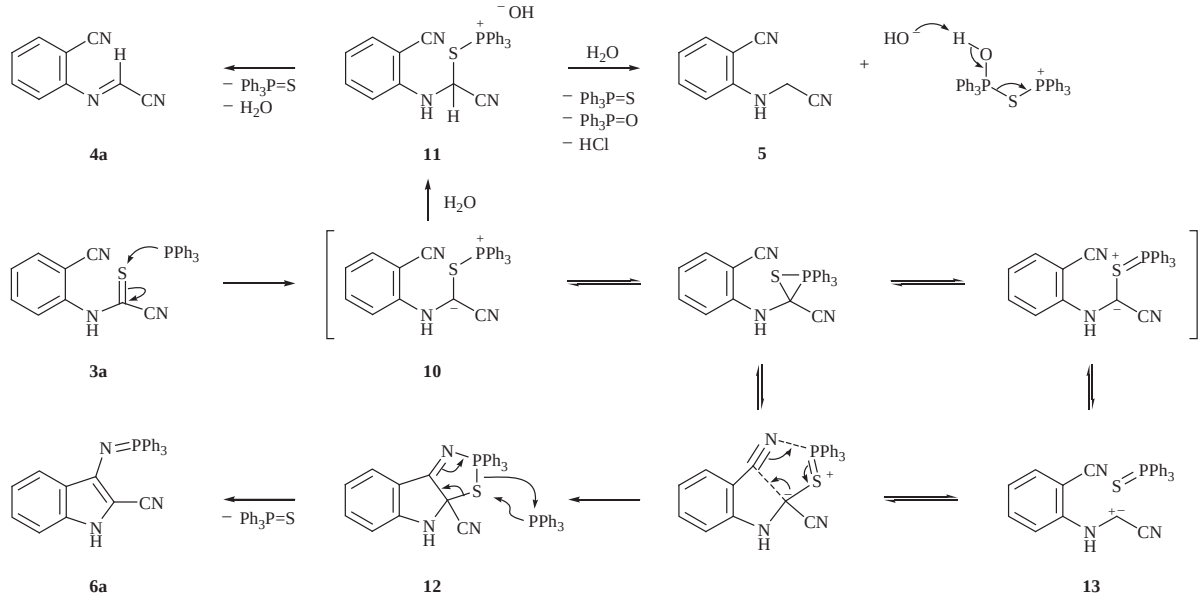
Thiophilic Ph_3P could attack the cyanothioformanilide **3** at sulfur then in the absence of water the zwitterion **10** could form, which would be expected to be in equilibrium with the thiaphosphirane, other ring opened zwitterionic forms and even possibly the carbene. Similar thiaphosphiranes, have previously been proposed[30] and recently the first single crystal X-ray structure of a thiaphosphirane was reported.[31] Protonation of the zwitterion **10** could generate a new phosphonium species **11** that could then suffer a second attack by Ph_3P on sulfur, followed by protonation, to release the observed (2-cyanomethylamino)benzonitrile **5**. Alternatively, the phosphonium species **11** could eliminate triphenylphosphine sulfide to give the observed imine **4a** although this could also form from the carbene **13** via a 1,2-H-shift (Scheme 4).

The formation of the indoles was more speculative. Tentatively the zwitterion **10** could add to the *ortho* cyano group either step-wise or via a cycloaddition to yield a heteroarene **12** that could fragment to the iminophosphorane **6a**. Hydrolysis of the iminophosphoranes **6a** can give the observed indole **2a** and we have shown previously that these two species can be readily inter-converted in high yield.[26] The proposed cycloadditions were tentatively supported by the high iminophosphorane recoveries in PhH and PhMe at reflux, while in MeOH and PTSA (1 equiv) the possibility that the *ortho*-cyano group was converted into an imidate prior to a step-wise cyclisation could explain the high yields of 3-aminoindole-2-carbonitrile **2a**. Attempts to improve the transformation in MeOH by replacing PTSA by mild Lewis acids such as caesium carbonate or zinc chloride gave mainly (2-cyanomethylamino)benzonitrile **5** in 65–67% yields. Further work to understand the scope of this transformation is now underway.

2.3. Scope of the 2-cyano cyanothioformanilides to 3-aminoindole-2-carbonitrile transformation

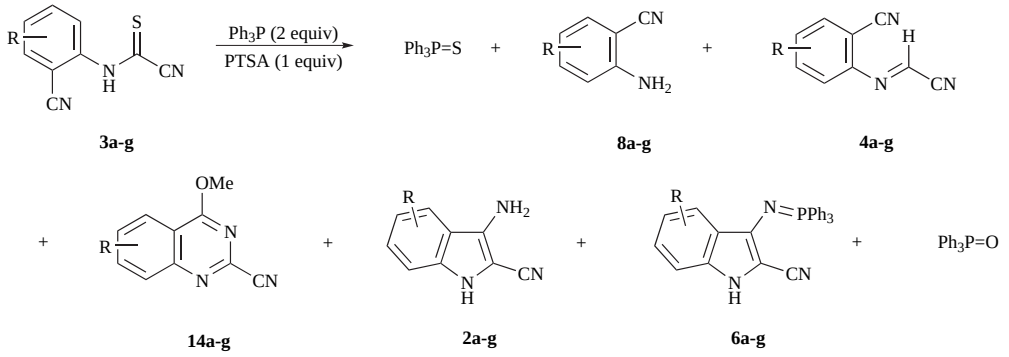
Elucidating the reaction mechanisms for the above transformations still requires further work, however, investigating the effect of aryl substituents can provide useful data as well as identifying the reaction scope and limitations. As such several aryl substituted 2-cyano cyanothioformanilides **3a**–**g** were treated with triphenylphosphine in MeOH in the presence of PTSA (1 equiv) at ca. 20 °C (Table 2).

In nearly all cases the expected 3-aminoindole-2-carbonitriles **2** were formed together with triphenylphosphine sulfide, triphenylphosphine oxide and some recovered substituted anthranilonitriles **8**. Some anomalous results were evident: First, the 2-cyano-4-nitro substituted cyanothioformanilide **3c** gave a mixture of 3-amino-5-nitroindole-2-cabonitrile **2c** (40%) together with the iminophosphorane **6c** (21%) but extending the reaction time to 6 h led to the latter's conversion into the 3-amino-5-nitroindole-2-cabonitrile **2c** (65%). Secondly, the 4-chloro-2-cyano cyanothioformanilide **3e** gave a moderate yield of 6-chloro-4-methoxyquinazoline-2-carbonitrile **14e** (23%). Finally, and the most notable exception, 2-cyano-4,5-dimethoxyphenyl cyanothioformanilide **2g** gave 4,5-dimethoxyanthranilonitrile **8g** (30%) and 4,6,7-trimethoxyquinazoline-2-carbonitrile **14g** (19%) and no indole products in MeOH. Nevertheless, in anhydrous PhMe at reflux in the absence of PTSA 2-cyano-4,5-dimethoxyphenyl cyanothioformanilide **3g** gave some



Scheme 4.

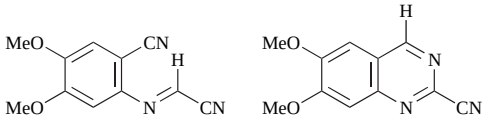
Table 2
Reaction of cyanothioformanilides **3a**–**g** (0.10 mmol) with Ph_3P (2 equiv) in the presence of PTSA (1 equiv) in wet MeOH at rt under a $CaCl_2$ drying tube



3a–**g** (R)	Time (h)	Yields (%)						
		Ph_3P=S	**8**	**4**	**14**	**2**	**6**	Ph_3P=O
3a (R=H)	0.17	72	**8a** (8)	**4a** (0)	**14a** (0)	**2a** (90)	**6a** (0)	80
3b (R=3-Me)	1	80	**8b** (24)	**4b** (0)	**14b** (0)	**2b** (75)	**6b** (0)	82
3c (R=4-O_2N)	1	77	**8c** (24)	**4c** (0)	**14c** (0)	**2c** (40)	**6c** (21)	78
3c (R=4-O_2N)	6	80	**8c** (25)	**4c** (0)	**14c** (0)	**2c** (65)	**6c** (0)	77
3d (R=5-Cl)	1	82	**8d** (26)	**4d** (0)	**14d** (0)	**2d** (72)	**6d** (0)	81
3e (R=4-Cl)	1	68	**8e** (0)	**4e** (0)	**14e** (23)	**2e** (75)	**6e** (0)	76
3f (R=5-MeO)	1	80	**8f** (37)	**4f** (0)	**14f** (0)	**2f** (63)	**6f** (0)	76
3g (R=4,5-(MeO)$_2$)	1	59	**8g** (27)	**4g** (0)	**14g** (19)	**2g** (0)	**6g** (0)	62
3g (R=4,5-(MeO)$_2$)	1[a]	52	**8g** (0)	**4g** (23)	**14g** (0)	**2g** (0)	**6g** (31)	50

[a] The reaction took place in PhMe at reflux.

(2-cyano-5,6-dimethoxyindol-3-yl)iminotriphenylphosphorane **6g** (31%) together with some 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **4g** (23%). While the 4-methoxy substituted quinazoline-2-carbonitriles have been previously prepared from cyanothioformanilides simply on treatment with base in MeOH,[6c] 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **4g** had previously mistakenly been identified as 6,7-dimethoxyquinazoline-2-carbonitrile **15**[26] and based on the above identification of 2-(cyanomethyleneamino)benzonitrile **4a** this tentative assignment was put into doubt (see below).



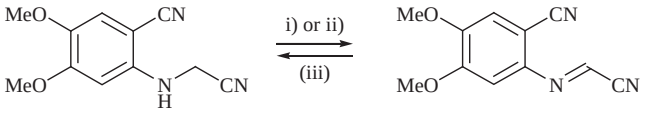
4g **15**

Since the by-products from the 2-cyano cyanothioformanilide **3** into indole **2** transformation were in some cases similar or identical to those isolated from the dithiazolimine **1** to indole **2** transformation it can be postulated that the latter transformation

involved a cyanothioformanilide intermediate or at least a closely related structure. The overall yields of the cyanothioformanilide to indole conversion were notably higher (63–90%) than those reported for the related dithiazolimine reaction (7–75%),[26] presumably owing to a shorter reaction pathway. Despite this, the dimethoxy substituted cyanothioformanilide **3g** gave very low yields of indoles [**2g** (0%), **3g** (31%)], similar to the analogous dithiazolimine reaction. Electron donating substituents such as methoxy groups clearly did not favour the formation of the anticipated indoles.

2.4. Independent synthesis of 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile 4g and 6,7-dimethoxyquinazoline-2-carbonitrile 15

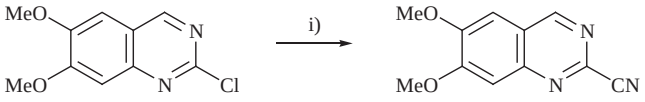
Unlike 2-(cyanomethyleneamino)benzonitrile **4a** the 4,5-dimethoxy analogue **4g** was considerably more stable and a sample was prepared independently via the mild oxidation of 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile **16** using either NBS or CaOCl.[32] Furthermore, treatment of 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **4g** with $NaBH_4$ in dry MeOH led to its facile conversion back to 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile **16** (Scheme 5).



16 **4g**

Scheme 5. Reagents and conditions: (i) NBS (1 equiv), $CaCl_2$ (0.5 equiv), $Ca(OH)_2$ (2.1 equiv) in CCl_4 at 55 °C, 2 d, (32%); (ii) CaOCl (1.5 equiv), $CaCl_2$ (0.2 equiv), $Ca(OH)_2$ (2 equiv) in DCM at rt, 4 d (50%); (iii) $NaBH_4$ (1.2 equiv) in dry MeOH, rt, 10 min (91%).

To eliminate any possibility of error a pure sample of 6,7-dimethoxyquinazoline-2-carbonitrile **15** was also prepared from 2-chloro-6,7-dimethoxyquinazoline **17**[33] using sodium cyanide (2 equiv) and DABCO (1 equiv) in DMSO (Scheme 6).[34]



17 **15**

Scheme 6. Reagents and conditions: (i) NaCN (2 equiv), DABCO (1 equiv) in DMSO at 75 °C, 10 h (38%), or at rt, 7 d (40%).

Differential scanning calorimetric studies (5 °C/min) of isomers **4g** and **15** gave considerably different thermal behaviour; the cyanomethyleneamino **4g** gave no melting point and only a decomposition peak at 177 °C (onset 175.4 °C) while the quinazoline **15** showed a sharp melting point at 303.4 °C (onset 301.3 °C) and was followed by an immediate decomposition at 310.3 °C (onset 305.7 °C). Furthermore, unlike the cyanomethyleneamino **4g** the isomeric 6,7-dimethoxyquinazoline-2-carbonitrile **15** was stable to $NaBH_4$ in dry MeOH. The spectral data of the independently prepared sample of isomer **4g** was identical to that isolated from the reaction of 2-cyano-4,5-dimethoxyphenyl cyanothioformanilide **3g** with triphenylphosphine.

3. Conclusions

2-Cyano cyanothioformanilide reacts with triphenylphosphine (2 equiv) in either MeOH in the presence of PTSA (1 equiv) or in refluxing toluene to give 3-amino indole-2-carbonitrile in good yield. The reaction in MeOH/PTSA tolerated electron withdrawing substituents but not the strongly electron releasing dimethoxy substituents on the arene moiety. Several minor by-products provided insight into a possible reaction mechanism. Furthermore, 2-(cyanomethyleneamino)benzonitrile treated with triphenylphosphine, PTSA in MeOH also surprisingly gave indole. The success of this transformation suggested that 2-cyano cyanothioformanilide could be an intermediate in the related triphenylphosphine mediated dithiazole to indole transformation.

4. Experimental

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 (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used throughout for all non-TLC scale chromatographic separations using Merck Silica Gel 60 (less than 0.063 mm).[35] Melting and decomposition points were determined using either a PolyTherm-A, Wagner & Munz, Koefler-Hotstage Microscope apparatus or where noted using a TA Instruments DSC Q1000 with samples hermetically sealed in aluminium pans under an argon atmosphere; using heating rates of 5 °C/min. Solvents used for recrystallisation are indicated after the melting point. UV spectra were obtained using a Perkin–Elmer Lambda-25 UV/vis spectrophotometer and inflections are identified by the abbreviation 'inf'. IR spectra were recorded on a Shimadzu FTIR–NIR Prestige-21 spectrometer with a Pike Miracle Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w, respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 machine (at 300 and 75 MHz, respectively). ^{13}C DEPT-135 NMR was used to identify quaternary and tertiary carbons, respectively. Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GC/MS with direct inlet probe. 2-Cyano cyanothioformanilides **3a**–**g**,[27] *N*-(2-cyanophenyl)formamide **9**[29] and 2-chloro-6,7-dimethoxyquinazoline **17**[33] were prepared according to literature procedures. The isolated reaction by-products, triphenylphosphine sulfide, triphenylphosphine oxide and the anthranilonitriles **8a**–**g** were identical to authentic samples.

4.2. Reaction of 2-cyano cyanothioformanilide 3a with Ph_3P (see Table 1)

To stirred solution of 2-cyano cyanothioformanilide **3a** (50 mg, 0.27 mmol) in dry PhH (2 mL) at ca. 20 °C, was added Ph_3P (142 mg, 0.54 mmol). The reaction mixture was then allowed to stir at ca. 20 °C for 5 min, until no starting materials remained (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane/DCM, 5:5) gave triphenylphosphine sulfide (134 mg, 84%) as colourless needles, mp 161–162 °C (from cyclohexane), R_f (hexane/DCM, 5:5) 0.60, identical to an authentic sample. Further elution (hexane/DCM, 2:8) gave 2-(cyanomethyleneamino)benzonitrile **4a** (4 mg, 11%) as colourless cotton fibres, mp 75–76 °C (from cyclohexane), R_f (hexane/DCM, 2:8) 0.70; (found: C, 69.7; H, 3.3; N, 27.0. $C_9H_5N_3$ requires C, 69.7; H, 3.3; N, 27.1%); λ_{max}(DCM)/nm 229 inf (log ε 3.03), 237 inf (3.08), 243 (3.12), 253 inf (2.96), 321 (2.54); ν_{max}/cm^{-1} 3096w, 3067w and 3032w (Ar CH), 2926w, 2234m (C≡N), 1599w, 1587w, 1570w, 1485m, 1447w, 1337m, 1283w, 1213w, 1188w, 1045w, 1005m, 932m, 874w, 853w, 762s, 733w; δ_H(300 MHz; $CDCl_3$)

7.78 (1H, dd, *J* 7.7, 1.5, Ph *H*-2 or 6), 7.68 (1H, ddd, *J* 7.9, 7.9, 1.4, Ph *H*-4 or 5), 7.62 (1H, s, C*H*=N), 7.50 (1H, ddd, *J* 7.7, 7.7, 0.9, Ph *H*-4 or 5), 7.18 (1H, d, *J* 8.1, Ph *H*-2 or 6); δ_C(75 MHz, $CDCl_3$) 150.6, 137.1 (Ph *C*H), 134.4 (Ph *C*H), 134.3 (Ph *C*H), 130.05 (*C*H), 118.3 (Ph *C*H), 116.2 (*C*≡N), 114.8 (*C*≡N), 109.25 (*C*C≡N); *m*/*z* (EI) 155 (M^+, 28%), 129 (M^+−CN, 8), 103 [M^+−2(CN), 100], 102 (26), 76 ($C_6H_4^+$, 30), 75 (27), 63 (7), 51 (17) and 2-(cyanomethylamino)benzonitrile **5** (16 mg, 38%) as light yellow needles, mp 95–96 °C (lit.,[36] 95–96 °C) (from cyclohexane/EtOH), R_f (hexane/DCM, 2:8) 0.50, identical to an authentic sample. Further elution (DCM, 100%) gave 3-aminoindole-2-carbonitrile **2a** (1 mg, 3%) as light yellow cotton fibres, mp 172–173 °C (lit.,[26] 172–173 °C) (from cyclohexane/EtOH), R_f (DCM, 100%) 0.50, identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 8:2) gave (2-cyanoindol-3-yl)iminotriphenylphosphorane **6a** (51 mg, 45%) as colourless prisms, mp 183–184 °C (lit.,[26] 183–183 °C) (from PhH), R_f (DCM/*t*-BuOMe, 8:2) 0.50, identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 7:3) gave triphenylphosphine oxide (103 mg, 69%) as colourless needles, mp 154–155 °C (from cyclohexane), R_f (DCM/*t*-BuOMe, 7:3) 0.50, identical to an authentic sample.

4.3. Reaction of 2-cyano cyanothioformanilides with triphenylphosphine and PTSA in MeOH. (Typical procedure) Table 2

To stirred solution of 2-cyano cyanothioformanilide **3a** (50 mg, 0.27 mmol) in MeOH (2 mL) at ca. 20 °C, was added PTSA (46.4 mg, 0.27 mmol) and the mixture was left to stir ca. 20 °C for 5 min. Then Ph_3P (142 mg, 0.54 mmol) was added and the mixture was then allowed to stir at ca. 20 °C for 50 min, until no starting materials remained (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane/DCM, 5:5) gave triphenylphosphine sulfide (114 mg, 72%) as colourless needles, mp 161–162 °C (from cyclohexane), R_f (hexane/DCM, 5:5) 0.60, identical to an authentic sample. Further elution (hexane/DCM, 3:7) gave anthranilonitrile (2.5 mg, 8%) **8a** as yellow prisms, mp 50–51 °C (from cyclohexane/EtOH), R_f (hexane/DCM, 3:7) 0.60, identical to an authentic sample. Further elution (DCM, 100%) gave 3-aminoindole-2-carbonitrile **2a** (38 mg, 90%) as light yellow cotton fibres, mp 172–173 °C (lit.,[26] 172–173 °C) (from cyclohexane/EtOH), R_f (DCM, 100%) 0.50, identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 7:3) gave triphenylphosphine oxide (120 mg, 80%) as colourless needles, mp 154–155 °C (from cyclohexane), R_f (DCM/*t*-BuOMe, 7:3) 0.50, identical to an authentic sample.

4.3.1. 3-Amino-4-methylindole-2-carbonitrile ***2b****.* (35 mg, 75%) yellow cotton fibres, mp 156–157 °C (lit.,[26] 156–157 °C) (from cyclohexane/EtOH) identical to an authentic sample.

4.3.2. 3-Amino-5-nitroindole-2-carbonitrile ***2c****.* (35.5 mg, 65%) red cotton fibres, mp 310–311 °C (lit.,[26] 310–311 °C) (from PhH) identical to an authentic sample.

4.3.3. N-(2-Cyano-5-nitroindol-3-yl)iminotriphenylphosphorane ***6c****.* (21 mg, 21%) red powder, mp>300 °C (from PhH); (found: C, 70.1; H, 4.1; N, 12.2. $C_{27}H_{19}N_4O_2P$ requires C, 70.1; H, 4.1; N, 12.1%); λ_{max}(DCM)/nm 231 (log ε 4.31), 294 (4.51), 332 inf (4.07); ν_{max}/cm^{-1} 3248w (NH), 2210m (C≡N), 1612w, 1576m, 1537s, 1468s, 1437m, 1396w, 1329s, 1310s, 1258m, 1180w, 1134w, 1109s, 1070m, 1016m, 997m, 897w, 870w, 854w, 841w, 818m, 756m, 741m, 733m, 719s; δ_H(300 MHz; CD_2Cl_2) 8.29 (1H, d, *J* 2.1, indole *H*-4), 8.07 (1H, br s, N*H*), 8.05 (1H, dd, *J* 9.2, 2.3, indole *H*-6), 7.84–7.77 (6H, m, PPh_3 *H*), 7.62–7.57 (3H, m, PPh_3 *H*), 7.54–7.48 (6H, m, PPh_3 *H*), 7.20 (1H, d, *J* 9.3, indole *H*-7); δ_C(75 MHz; CD_2Cl_2) 143.5, 141.3, 139.2, 133.0 (d, J_{PC} 9.8, Ph_3P *C*-3), 132.6 (d, J_{PC} 3.0, Ph_3P *C*-4), 131.0 (d, J_{PC} 101.3, Ph_3P *C*-1), 129.2 (d, J_{PC} 12.7, Ph_3P *C*-2), 124.7 (d, J_{PC} 12.8, indole *C*-3), 121.2 (indole *C*H), 119.3 (indole *C*H), 116.2 (*C*≡N), 111.8 (indole *C*H), 97.6 (d, J_{PC} 12.8, indole *C*-2, *C*C≡N); δ_P(121.5 MHz; DMSO-d_6) 6.59; *m*/*z* (EI) 462 (M^+, 100%), 436 (M^+−CN, 8), 435 (8), 416 (5), 415 (9), 390 (3), 262 (PPh_3^+, 6), 231 (5), 208 (6), 183 (47), 152 (6), 133 (2), 108 (8).

4.3.4. 3-Amino-5-chloroindole-2-carbonitrile ***2d****.* (37 mg, 72%) light red powder, mp 190–191 °C (lit.,[26] 190–191 °C) (from EtOH) identical to an authentic sample.

4.3.5. 3-Amino-6-chloroindole-2-carbonitrile ***2e****.* (39 mg, 75%) red powder, mp 210–211 °C (lit.,[26] 210–211 °C) (from EtOH) identical to an authentic sample.

4.3.6. 6-Chloro-4-methoxyquinazoline-2-carbonitrile ***14e****.* (12 mg, 23%) as colourless fibres, mp 139–140 °C (from cyclohexane); (found: C, 54.7; H, 2.8; N, 19.2. $C_{10}H_6ClN_3O$ requires C, 54.7; H, 2.8; N, 19.1%); λ_{max}(DCM)/nm 237 (log ε 4.46), 309 inf (3.80), 322 inf (3.40); ν_{max}/cm^{-1} 3092w (Ar CH), 2963w, 2241w (C≡N), 1609w, 1570s, 1553m, 1499s, 1460m, 1499s, 1346w, 1294m, 1221w, 1190m, 1146w, 1130m, 1074m, 988m, 951s, 891m, 835s, 814m, 791m; δ_H(300 MHz; $CDCl_3$) 8.14 (1H, d, *J* 2.1, *H*-5), 7.93 (1H, d, *J* 9.0, *H*-8), 7.85 (1H, dd, *J* 8.9, 2.3, *H*-7), 4.23 (3H, br s, CH_3O); δ_C(75 MHz; $CDCl_3$) one peak missing 166.8, 148.8, 139.7, 135.7 (Ar *C*H), 129.9 (Ar *C*H), 122.9 (Ar *C*H), 117.5, 115.9, 55.7 (*C*H_3O); *m*/*z* (EI) 221 (M^++2, 35%), 219 (M^+, 100), 190 (41), 184 (83), 162 (15), 149 (16), 139 (32), 137 (80), 126 (18), 124 (28), 111 (23), 100 (29), 97 (31), 85 (41), 75 (27), 71 (53), 57 (94).

4.3.7. 3-Amino-6-methoxyindole-2-carbonitrile ***2f****.* (32 mg, 63%) red prisms, mp 179–180 °C (lit.,[26] 179–180 °C) (from cyclohexane/EtOH) identical to an authentic sample.

4.3.8. 4,6,7-Trimethoxyquinazoline-2-carbonitrile ***14g****.* (9 mg, 19%) yellow needles, mp 228–229 °C (lit.,[6c] 238 °C) (from cyclohexane/EtOH); (found: C, 58.8; H, 4.6; N, 17.1. $C_{12}H_{11}N_3O_3$ requires C, 58.8; H, 4.5; N, 17.1%); λ_{max}(DCM)/nm 248 (log ε 4.65), 263 inf (4.32), 303 inf (4.05), 313 (4.12), 328 (4.05); ν_{max}/cm^{-1} 3011w (Ar CH), 2986w and 2943w, 2237w (C≡N), 1611m, 1578m, 1558w, 1504m, 1481s, 1454w, 1433m, 1420m, 1410m, 1375m, 1315w, 1267s, 1250s, 1223m, 1213m, 1182m, 1167m, 1105m, 1022m, 999s, 947m, 862m, 847m, 789m, 764w; δ_H(300 MHz; $CDCl_3$) 7.37 (1H, s, *H*-5 or 8), 7.29 (1H, s, *H*-5 or 8), 4.19 (3H, s, CH_3O), 4.04 (3H, s, CH_3O), 4.03 (3H, s, CH_3O); δ_C(75 MHz; $CDCl_3$) 165.7, 156.1, 151.7, 147.9, 138.1, 116.5, 111.6, 107.0 (Ar *C*H), 101.1 (Ar *C*H), 56.5 (*C*H_3O), 56.4 (*C*H_3O), 55.0 (*C*H_3O); *m*/*z* (EI) 245 (M^+, 100%), 230 (M^+−CH_3, 21), 216 (23), 202 (7), 174 (6), 159 (6), 145 (6), 131 (6), 97 (8), 77 (9), 67 (17), 57 (12).

4.4. Reaction of 2-(cyanothioformamido)-4,5-dimethoxybenzonitrile 3f with triphenylphosphine in dry toluene (see Table 2)

To a stirred solution of 2-(cyanothioformamido)-4,5-dimethoxybenzonitrile **3f** (67 mg, 0.27 mmol) in toluene (2 mL) at ca. 20 °C, was added Ph_3P (142 mg, 0.54 mmol) in one portion. The mixture was then heated to 110 °C for 1 h, until no starting material remained (TLC) and adsorbed onto silica. Chromatography (hexane/DCM, 5:5) gave triphenylphosphine sulfide (61 mg, 52%) as colourless needles, mp 161–162 °C (from cyclohexane), R_f (hexane/DCM, 2:8) 0.60, identical to an authentic sample. Further elution (DCM, 100%) gave 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **4g** (10 mg, 23%) as yellow cotton fibres, mp 170–171 °C (from cyclohexane) (DSC: onset 175.4 °C, peak 177.0 °C), R_f (DCM, 100%) 0.50 (found: C, 61.4; H, 4.2; N, 19.5. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%); λ_{max}(DCM)/nm 228 (log ε 3.02), 235 (3.21), 261 (3.35), 285 inf (2.88), 363 (3.02); ν_{max}/cm^{-1} 2920w, 2230m (C≡N), 1597m, 1547m, 1537m, 1516s, 1464m, 1368m, 1287s, 1231s,

1198m, 1109s, 1026m, 993s, 908w, 876m, 837m; δ_H(300 MHz; DMSO-d_6) 8.17 (1H, s, N=C*H*), 7.51 (1H, s, Ph *H*), 7.31 (1H, s, Ph *H*) 3.87 (3H, s, CH_3O), 3.86 (3H, s, CH_3O); δ_C(75 MHz; DMSO-d_6) 152.9, 150.2, 143.9, 137.4 (Ar *C*H), 116.8, 116.0, 114.5 (Ar *C*H), 102.2, 101.8 (Ar *C*H), 56.4 (*C*H_3O), 56.3 (*C*H_3O); *m*/*z* (EI) 215 (M^+, 100%), 200 (72), 172 (33), 157 (5), 145 (74), 129 (11), 117 (25), 104 (29), 102 (49), 90 (39), 88 (23), 78 (57), 76 (58), 64 (33), 53 (30). Further elution (DCM/*t*-BuOMe, 8:2) gave triphenylphosphine oxide (55 mg, 50%) as colourless needles, mp 154–155 °C (from cyclohexane), R_f (DCM/*t*-BuOMe, 8:2) 0.50, identical to an authentic sample. Further elution (hexane/EtOH, 7:3) gave (*2-cyano-5,6-dimethoxyindol-3-yl*) *iminotriphenylphosphorane* **6g** (30 mg, 31%) as red prisms, mp 157–158 °C (from cyclohexane/EtOH), R_f (hexane/EtOH, 7:3) 0.60; (found: C, 73.0; H, 5.1; N, 8.8. $C_{29}H_{24}N_3O_2P$ requires C, 73.0; H, 5.1; N, 8.8%); λ_{max}(DCM)/nm 230 (log ε 3.47), 256 (3.22), 318 (3.22), 351.5 inf (2.79); ν_{max}/cm^{-1} 3057w, 3015w, 2926w, 2193m (C≡N), 1630w, 1518s, 1477s, 1450w, 1437s, 1329m, 1294s, 1250m, 1227m, 1204w, 1194s, 1173m, 1144m, 1111s, 1016m, 993m, 988m, 932m, 841m, 802m, 750m, 745m, 718s; δ_H(300 MHz; CD_2Cl_2) 7.80–7.73 (6H, m, Ph_3P *H*), 7.65 (1H, br s, N*H*), 7.60–7.54 (3H, m, Ph_3P *H*), 7.50–7.45 (6H, m, Ph_3P *H*), 6.63 (1H, s, indole *H*-4 or 7), 6.54 (1H, s, indole *H*-4 or 7), 3.78 (3H, s, CH_3O), 3.45 (3H, s, CH_3O); δ_C(75 MHz; CD_2Cl_2) 150.7, 145.3, 141.5, 133.0 (d, J_{PC} 9.8, Ph_3P *C*-3), 132.7, 132.3 (d, J_{PC} 3.0, Ph_3P *C*-4), 132.0 (d, J_{PC} 100.5, Ph_3P *C*-1), 129.0 (d, J_{PC} 12.0, Ph_3P *C*-2), 117.7 (d, J_{PC} 2.3, indole *C*≡N), 117.3 (d, J_{PC} 9.0 indole *C*-3), 102.3 (indole *C*H), 95.7 (d, J_{PC} 15.8, indole *C*-2, *C*C≡N), 94.5 (indole *C*H), 56.1 (*C*H_3O), 56.0 (*C*H_3O); δ_P(121.5 MHz; CD_2Cl_2) 4.0; *m*/*z* (EI) 477 (M^+, 100%), 462 (4), 435 (8), 292 (6), 265 (17), 262 (8), 239 (7.5), 183 (37), 108 (14), 77 (3).

4.5. 2-(Cyanomethyleneamino)-4,5-dimethoxybenzonitrile 4g via oxidation of 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile 16

4.5.1. Using NBS. To a stirred solution of NBS (27 mg, 0.20 mmol) in CCl_4 (1 mL) at ca. 55 °C, was added a solution of 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile **16** (36 mg, 0.20 mmol) in CCl_4 (1 mL). The mixture was left to stir at ca. 55 °C for 5 min and then $Ca(OH)_2$ (31 mg, 0.42 mmol) and $CaCl_2$ (11 mg, 0.1 mmol) were added to the solution. The mixture was left to stir at this temperature for 2 d until no starting material remained (TLC) and the mixture was then adsorbed onto silica. Chromatography (DCM, 100%) gave 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **4g** (14 mg, 32%) as yellow cotton fibres, mp 170–171 °C (from cyclohexane), R_f (DCM, 100%) 0.50, identical that described above.

4.5.2. Using calcium hypochlorite. To a stirred solution of 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile **16** (36 mg, 0.20 mmol) in DCM (2 mL) was added CaOCl (43 mg, 0.30 mmol) and $CaCl_2$ (11 mg, 0.10 mmol). The mixture was left to stir at ca. 20 °C for 5 min and then $Ca(OH)_2$ (30 mg, 0.40 mmol) was added to the solution. The mixture was left to stir at this temperature for 4 d until no starting material remained (TLC) and then adsorbed onto silica. Chromatography (DCM, 100%) gave 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **4g** (21.5 mg, 50%) as yellow cotton fibres, mp 170–171 °C (from cyclohexane), R_f (DCM, 100%) 0.50, identical to that described above.

4.6. 2-(Cyanomethylamino)-4,5-dimethoxybenzonitrile 16 via reduction of 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile 4g

To a stirred solution of 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **4g** (20 mg, 0.09 mmol) in dry MeOH (2 mL) at ca. 20 °C, was added $NaBH_4$ (4 mg, 0.11 mmol). The mixture was then left to stir at ca. 20 °C for 10 min until no starting material remained (TLC). The mixture was then extracted with DCM (20 mL). The combined organic layers were dried (Na_2SO_4) and filtered to afford the *title compound* **16** (18 mg, 91%) as colourless cotton fibres, mp 143–144 °C (lit.,[36] 143–144 °C) (from cyclohexane/EtOH) identical to an authentic sample.

4.7. 6,7-Dimethoxyquinazoline-2-carbonitrile 15

To a stirred solution of 2-chloro-6,7-dimethoxyquinazoline **17** (30 mg, 0.134 mmol) in DMSO (2 mL) at ca. 20 °C, were added DABCO (15 mg, 0.134 mmol) and NaCN (13 mg, 0.268 mmol). The mixture was left to warm at 80 °C for 10 h until no starting material remained (TLC). On cooling to rt the mixture was diluted with water (20 mL) and extracted with DCM (3×20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo to give a pale yellow solid reside. Chromatography (DCM, 100%) gave the *title compound* **15** (11 mg, 38%) as a colourless powder, mp 300–301 °C (from EtOH) (DSC: onset 301.3 °C, peak 303.4 °C), R_f (DCM, 100%) 0.60; (found: C, 61.3; H, 4.1; N, 19.5. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%); λ_{max}(DCM)/nm 230 (log ε 2.96), 255 (3.35), 299 inf (2.44), 324 (2.58), 338 (2.71); ν_{max}/cm^{-1} 3059w, 2986w, 2955w, 2239w (C≡N), 1611m, 1568m, 1560w, 1501s, 1476w, 1445m, 1427s, 1412m, 1389w, 1342m, 1288m, 1256s, 1240m, 1219m, 1167s, 1096w, 1022m, 997s, 951m, 870s, 841m, 789m; δ_H(300 MHz; DMSO-d_6) 9.43 (1H, s, *H*-4), 7.65 (1H, s, *H*-5 or 8), 7.53 (1H, s, *H*-5 or 8), 4.02 (3H, s, CH_3O), 3.99 (3H, s, CH_3O); δ_C(75 MHz; DMSO-d_6) 157.9 (*C*-4), 157.4, 152.5, 147.4, 138.5, 121.7, 117.1 (*C*≡N), 106.2 (Ar *C*-5 or 8), 105.1 (Ar *C*-5 or 8), 56.7 (*C*H_3O), 56.4 (*C*H_3O); *m*/*z* (EI) 215 (M^+, 100%), 200 (19), 172 (19), 145 (13), 120 (23), 117 (8), 102 (6), 92 (13), 90 (11), 77 (10), 65 (12).

4.8. Reaction of 2-(cyanomethyleneamino)benzonitrile 4a with Ph_3P, PTSA in MeOH

To a stirred solution of 2-(cyanomethyleneamino)benzonitrile **4a** (20 mg, 0.13 mmol) and PTSA (24.5 mg, 0.13 mmol) in MeOH (2 mL) at ca. 20 °C, was added in one portion Ph_3P (68 mg, 0.26 mmol). The mixture was left to stir at this temperature for 5 h, until no starting material remained (TLC) and then adsorbed onto silica. Chromatography (hexane/DCM, 5:5) gave unreacted Ph_3P (40 mg, 59%) as colourless flakes, mp 80–81 °C (from cyclohexane), R_f (hexane/DCM, 5:5) 0.70, identical to an authentic sample. Further elution (hexane/DCM, 2:8) gave anthranilonitrile **8a** (2 mg, 13%) as yellow prisms, identical to an authentic sample. Further elution (DCM, 100%) gave 3-aminoindole-2-carbonitrile **2a** (6 mg, 30%) as light yellow cotton fibres, mp 172–173 °C (lit.,[26] 172–173 °C) (from cyclohexane/EtOH), R_f (DCM, 100%) 0.50, identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 9:1) gave *N*-(2-cyanophenyl)formamide **9** (10 mg, 53%) as yellow fibres, mp 121–122 °C (lit.,[37] 125–127 °C) (from Et_2O), R_f (DCM/*t*-BuOMe, 9:1) 0.45; ν_{max}/cm^{-1} 3260w (NH), 2220m (C≡N), 1711m, 1668s, 1585s, 1537s, 1450s, 1404s, 1358w, 1302s, 1258w, 1165m, 1038w, 947w, 864m; δ_H(300 MHz; DMSO-d_6) 10.39 (1H, br s, N*H*), 8.35 (1H, s, C*HO*), 7.91 (1H, d, *J* 8.1, Ph *H*-3 or 6), 7.82 (1H, d, *J* 7.5, Ph *H*-3 or 6), 7.69 (1H, dd, *J* 7.8, 7.7, Ph *H*-4 or 5), 7.33 (1H, dd, *J* 7.8, 7.7, Ph *H*-4 or 5); *m*/*z* (EI) 146 (M^+, 24%), 118 (100), 91 (50), 64 (19), 57 (13), identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 8:2) gave triphenylphosphine oxide (13 mg, 35%) as colourless needles, mp 154–155 °C (from cyclohexane), R_f (DCM/*t*-BuOMe, 8:2) 0.50, identical to an authentic sample.

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Supplementary data

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