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

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ABSTRACT

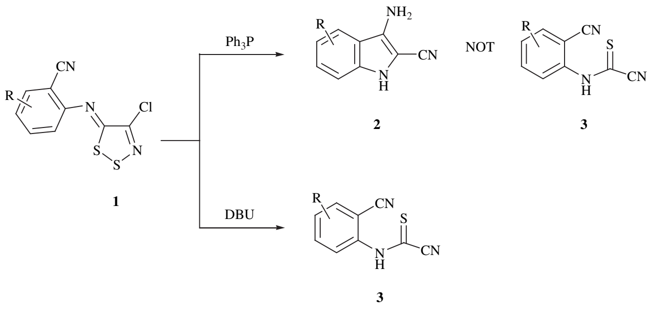
2-Cyano cyanothioformanilide **3a** reacts with triphenylphosphine in the presence of water to give 2-(cyanomethyleneamino)benzonitrile **4a**, 2-(cyanomethylamino)benzonitrile **5**, 3-aminoindole-2-carbonitrile **2a** and (2-cyanoindol-3-yl)iminotriphenylphosphorane **6a**. In the presence of *p*-toluenesulfonic 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.

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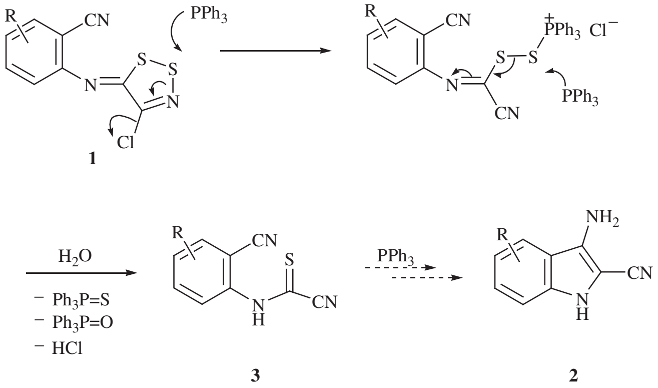
While a mechanism was not put forward for the formation of the indoles **2**, our initial thoughts focused on the triphenylphosphine behaving as a typical thiophile and attacking the dithiazolimine S-2 ring sulfur (Scheme 2). This would be expected to lead to the 2-cyano cyanothioformanilide **3**, however,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

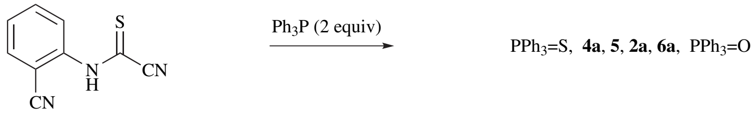
2.1. Reaction of 2-cyano cyanothioformanilides with triphenylphosphine

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**.

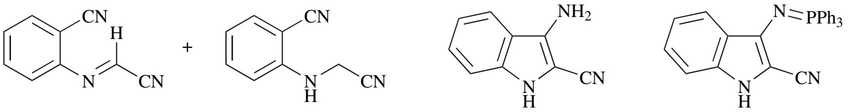
2-(Cyanomethyleneamino)benzonitrile **4a** was obtained as colourless cotton fibres, mp 75–76 °C (from cyclohexane). Microanalysis and mass spectrometry supported the formula $C_9H_5N_3$ [*m*/*z* 155 (M^+, 28%)]. The presence of a cyano group was supported by an IR band at 2234 cm^{-1} and stretching 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



3a



4a **5** **2a** **6a**

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.