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Unexpected behavior of the reaction between acyl thioformanilides and acetonitrile derivatives—a useful entry to new penta-substituted dipyrrole disulfides

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ABSTRACT

A convenient and unexpected synthesis of penta-substituted dipyrrole disulfides starting from readily available acyl thioformanilides and acetonitrile derivatives has been developed. The overall process leads to the creation of two C–C bonds, two C–N bonds, and one S–S bond with the concomitant formation of two pyrrole rings and disulfide from the fact that only two reagents need to be mixed together, and it complements the existing pyrrole disulfides chemistry.

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The S–S bond functional group exists not only in proteins, but also in numerous natural products.[1] Modern methods for the formation of S–S bond are required for the synthesis of many biologically active compounds involved in chemical and biological processes. The pyrrole core is a structural motif of particular interest in the fields of natural products, medicinal chemistry, and material science.[2] A variety of synthetic methods for the preparation of disulfides[3] and pyrroles[4] have been developed owing to their wide range of activities and importance. Surprisingly, there are only two examples bearing both characteristic groups together that have been employed to give dipyrrol disulfides.[5] However, these methods suffer from high toxicity, low overall yields, and relatively inaccessible starting materials used.

Acyl thioformanilides **1**[6] are versatile building blocks in organic synthesis owing to their ready accessibility and good reactivity. The chemical properties of precursors **1** are determined by the four active centers. Two nucleophilic centers are localized on the heteroatoms, the other two electrophilic centers are associated with the carbon atoms of carbonyl and thiocarbonyl groups. This behavior makes it an important candidate for developing a new synthetic strategy in medicinal and material chemistries.

In connection with our methodology of ongoing project on the development of novel heterocyclic compounds,[7] we had occasion to examine the cross-condensation of **1** with acetonitrile derivatives. Surprisingly, a new type of penta-substituted dipyrrole disulfides **4** was found as a major product along with the formation of a small amount of the monosulfides **5**. The products **4** were easily separated from **5** by recrystallization or flash chromatography (Scheme 1).

So far, to the best of our knowledge, there have been no reports on the synthetic application of acyl thioformanilides **1** with acetonitrile derivatives. The results of our studies, which led to an unprecedented synthesis of penta-substituted dipyrrole disulfides, are presented herein.

In initial studies, we first envisioned the reaction of the precursor 2-oxo-*N*,2-diphenylethanethioamide **1a** with ethyl 2-cyanoacetate **2** in the presence of base at room temperature. Notably, the reaction of the anion of **2** with **1a** regioselectively affords a novel and unexpected hydroxylated product **3a**, ethyl 2-amino-4-hydroxy-1,4-diaryl-5-thioxo-4,5-dihydro-1*H*-pyrrole-3-carboxylate, but not the corresponding dehydrated product. The intermediate **3a** was subsequently characterized by IR, ^{1}H NMR, ^{13}C NMR, HMBC, HMQC, and MS analysis.[8]

Interestingly, the unexpected compounds bis(2-amino-1,4-diphenyl-3-ethoxycarbonyl-1*H*-pyrrole-5-yl)disulfide **4a** and bis(2-

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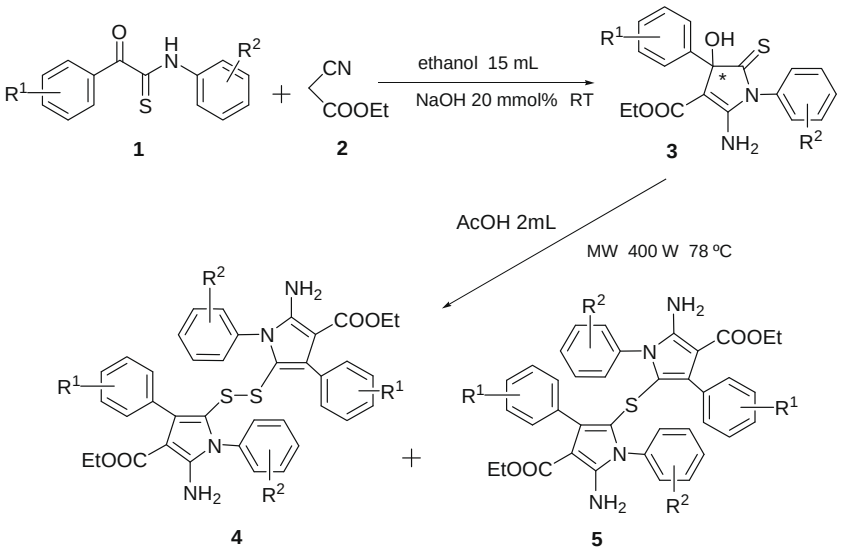


Scheme 1. Couplings of acyl thioformanilide **1** with ethyl 2-cyanoacetate **2** to disulfides.

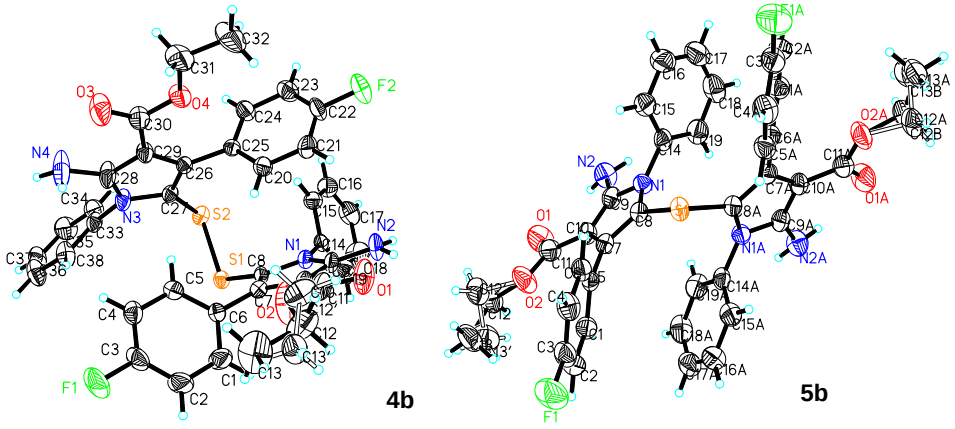
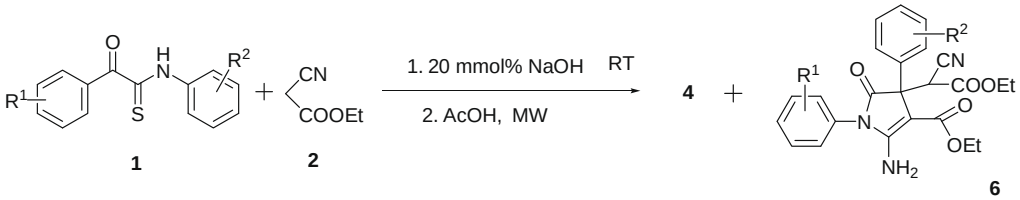


Figure 1. The structures of compounds **4b** and **5b**. Displacement ellipsoids are drawn at the 30% probability level.

Table 1
One-pot reactions to obtain disulfides[a]



Entry	1	R^1	R^2	Time	Product (yield, %)
1	**1a**	H	H	2.5 h[b], 5 min[c]	**4a** (46) **6a** (8)
2	**1b**	*p*-F	H	1.5 h[b], 5 min[c]	**4b** (53) **6b** (trace)
3	**1c**	*p*-Cl	H	2 h[b], 5 min[c]	**4c** (51) **6c** (10)
4	**1d**	*p*-Br	H	2 h[b], 5 min[c]	**4d** (49) **6d** (trace)
5	**1e**	*p*-OCH_3	H	3 h[b], 5 min[c]	**4e** (41) **6e** (8)
6	**1f**	*p*-CH_3	H	3 h[b], 5 min[c]	**4f** (43) **6f** (9)
7	**1g**	*o*-F	H	2 h[b], 5 min[c]	**4g** (34) **6g** (trace)
8	**1h**	*p*-F	*p*-OCH_3	0.5 h[b], 3 min[c]	**4h** (55) **6h** (7)
9	**1i**	*p*-F	*p*-NO_2	4.5 h[b], 5 min[c]	**4i** (45) **6i** (6)
10	**1j**	*p*-Cl	*p*-OC_2H_5	0.4 h[b], 5 min[c]	**4j** (54) **6j** (trace)
11	**1k**	*p*-CH_3	*p*-OC_2H_5	5 h[b], 5 min[c]	**4k** (31) **6k** (trace)
12	**1l**	*p*-CH_3	*p*-Cl	5 h[b], 5 min[c]	**4l** (28) **6l** (4)

[a] Reaction condition: acyl thioformanilide (3 mmol), ethyl 2-cyanoacetate (3 mmol), EtOH (15 mL), catalyst.
[b] The first step, 20 mmol % NaOH, rt.
[c] The second step, AcOH, MW, 400 W, 60 °C.

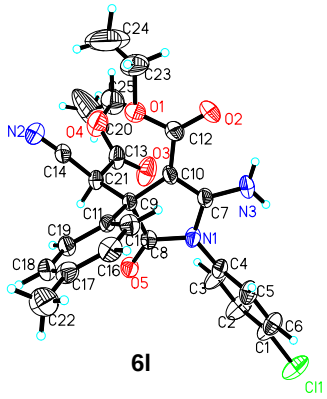


Figure 2. The structure of compound **6l**. Displacement ellipsoids are drawn at the 30% probability level.

amino-1,4-diphenyl-3-ethoxycarbonyl-1*H*-pyrrole-5-yl) monosulfide **5a** were obtained when acetic acid (2 mL) was added to **3a** under conventional heating, but the yields were only 27% and 3%, respectively.

The effect of solvents (C_2H_5OH, CH_3OH, CH_3CN, THF, and DMSO) was investigated using the reaction of **1a** and **2** as model reaction by employing 20 mmol % NaOH as the catalyst. The results showed that C_2H_5OH is the best solvent. We attempted to change the amount of NaOH, and use of 20 mmol % NaOH relative to acyl thioformanilide was the best choice. Moreover, NaOH was the most effective catalyst compared to another two bases, Et_3N and Na_2CO_3. Another two acids 10% HCl and $ZnCl_2$ for the second step were also tested, but the yields of disulfide **4a** were only 20% and 23%, respectively, lower than that in acetic acid.

Encouraged by this successful transformation from **3a** to **4a**, we tested this protocol for the synthesis of other disulfide derivatives using various **1** and **2**. The results showed that all reactions produced penta-substituted dipyrrole disulfides **4** as the major product along with the formation of a small amount of the monosulfides **5**. The structures of **4b**, **4h**, and **5b** were confirmed by X-ray crystallographic analysis (Fig. 1).

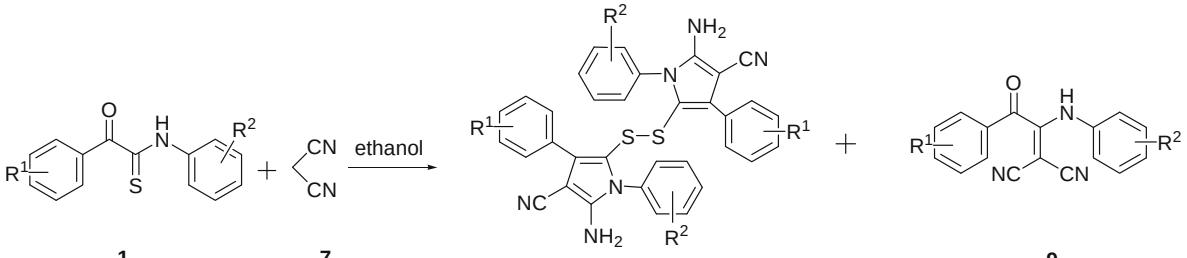
From a synthetic point of view, one-pot procedures beginning with simple substrate provide ideal strategies for the formation of target molecules. In order to improve the yields of the disulfides **4**, we attempted to combine the two-step reactions in a one-pot sequence without the isolation of intermediates **3**.

At the end of the condensation of **1** with **2**, acetic acid (2 mL) was added to the mixture solution under microwave irradiation. Similarly, the desired products **4** were the major products with higher yields, but an unexpected white solid, ethyl 2-amino-4-(1-cyano-2-ethoxy-2-oxoethyl)-5-oxo-1,4-diaryl-4,5-dihydro-1*H*-pyrrole-3-carboxylates **6**, and ABB′3CR[9] products were formed as the minor adducts, which correspond to the reaction of the remaining **2** with **3** (Table 1). The structural determination of **6l** was achieved following their spectral data and X-ray single crystal diffraction analysis (Fig. 2).

As shown in Table 1, the methodology was tolerant of a variety of electronically different para substituents (Table 1, entries 1–6) to compounds **1**. Different derivatives of **1** with a variety of different R^1 and R^2 substituents were also submitted to reaction conditions to consistently provide the corresponding disulfides (Table 1, entries 8–12). Notably, for substrates **1** with an electron-withdrawing R^1 group and an electron-donating R^2 group, the desired disulfides were afforded in higher yields and shorter time (Table 1, entries 8 and 10).

The simplicity of the described reaction prompted us to explore the scope and generality of this reaction. We further chose to

Table 2
One-pot couplings of acyl thioformanilide **1** with malononitrile **7**[a]



1 **7** **8** **9**

Entry	1	R^1	R^2	Time	Product (yield, %)
1	**1a**	H	H	5 h[b], 5 min[c]	**8a** (30) **9a** (trace)
2	**1a**	H	H	2 h[d], 5 min[c]	**8a** (35) **9a** (trace)
3	**1a**	H	H	10 min[e]	**8a** (50) **9a** (trace)
4	**1a**	H	H	5 min[f]	**8a** (38) **9a** (trace)
5	**1b**	*p*-F	H	10 min[e]	**8b** (56) **9b** (12)
6	**1c**	*p*-Cl	H	5 min[e]	**8c** (54) **9c** (trace)
7	**1d**	*p*-Br	H	15 min[e]	**8d** (52) **9d** (10)
8	**1e**	*p*-OCH_3	H	20 min[e]	**8e** (43) **9e** (10)
9	**1f**	*p*-CH_3	H	15 min[e]	**8f** (46) **9f** (trace)
10	**1h**	*p*-F	*p*-OCH_3	10 min[e]	**8h** (58) **9h** (8)

[a] Reaction condition: acyl thioformanilide (3 mmol), malononitrile (3 mmol), solvent (15 mL).
[b] The first step, 0.2 equiv NaOH, −20 °C.
[c] The second step, MW, 400 W, 60 °C, acetic acid (2 mL).
[d] 0.5 equiv NaOH, −20 °C.
[e] 1 equiv NaOH, −20 °C.
[f] 1.5 equiv NaOH, −20 °C.

investigate the reactions of **1** with malononitrile **7** at low temperature (−20 °C) (Table 2).

Interestingly, when 1 equiv of NaOH was added to the solution of **1** and **7**, disulfides **8** were directly obtained from the mixture with moderate yield of 50% without the addition of acetic acid. However, the minor amount of H_2S-released adducts 2-(2-oxo-2-aryl-1-(arylamino) ethylidene)malononitriles **9** was also observed, but the monosulfides were not observed. The structure of **8a** was confirmed by X-ray single crystal diffraction analysis (Fig. 3).

A possible mechanism for this reaction is proposed in Scheme 2. Firstly, a proton of ethyl 2-cyanoacetate **2** is deprived by NaOH to produce a carbon nucleophilic center **A**, which attacks the carbon of carbonyl group of **1** to give **B**. An intramolecular cyclization is conducted by nucleophilic attack of the nitrogen in **B** to the triple bond in the CN group, then rearrangement leads to the isolated **3,** which as a highly reactive intermediate, featuring a hydroxy group at the α-position of thiocarbonyl group, is essential for this reaction to take place. Then, intermediate **3** might undergo a [1,3] hydroxyl migration to form the pyrrole sulfenic acid **C,** which could not be trapped because of its high reactivity, but it has been implicated as key intermediate in a wide variety of reactions including biological transformation.[10] Finally, the sulfenic acids **C** are converted to dimmers **4** by releasing of hydrogen peroxide according to the results reported by Davis et al.[11] Although we have not established the mechanism of this reaction in an experimental manner, it actually provides an efficient and unusual synthetic entry into a new class of penta-substituted dipyrrole disulfides based on the reaction of acyl thioformanilides and acetonitrile derivatives.

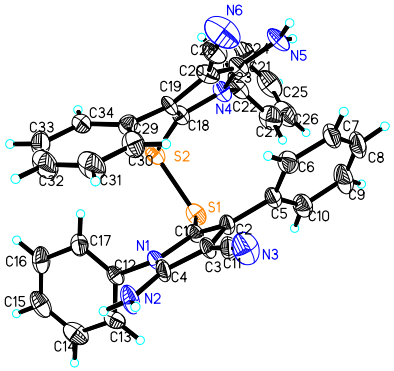


Figure 3. The structure of compound **8a**. Displacement ellipsoids are drawn at the 30% probability level.

In conclusion, we have characterized and determined the structure of a highly unusual and quite unexpected products of a simple reaction that result in the formation of elaborate substructures, namely, the disulfide moiety and pyrrole structure motif systems. The process, which leads to the creation of two C–C bonds, two C–N bonds, and one S–S bond with the concomitant formation of two pyrrole rings and disulfide from the fact that only two reagents need to be mixed together, complements the existing pyrrole and disulfides chemistries. Although the reaction yields are moderate, it is an entirely new approach for the conversion of acyl thioformanilides and active methylene compounds into a novel penta-substituted dipyrrole disulfides structural motifs. Effort is in progress to elucidate further the mechanistic details of these reactions and understand their scope and limitations.

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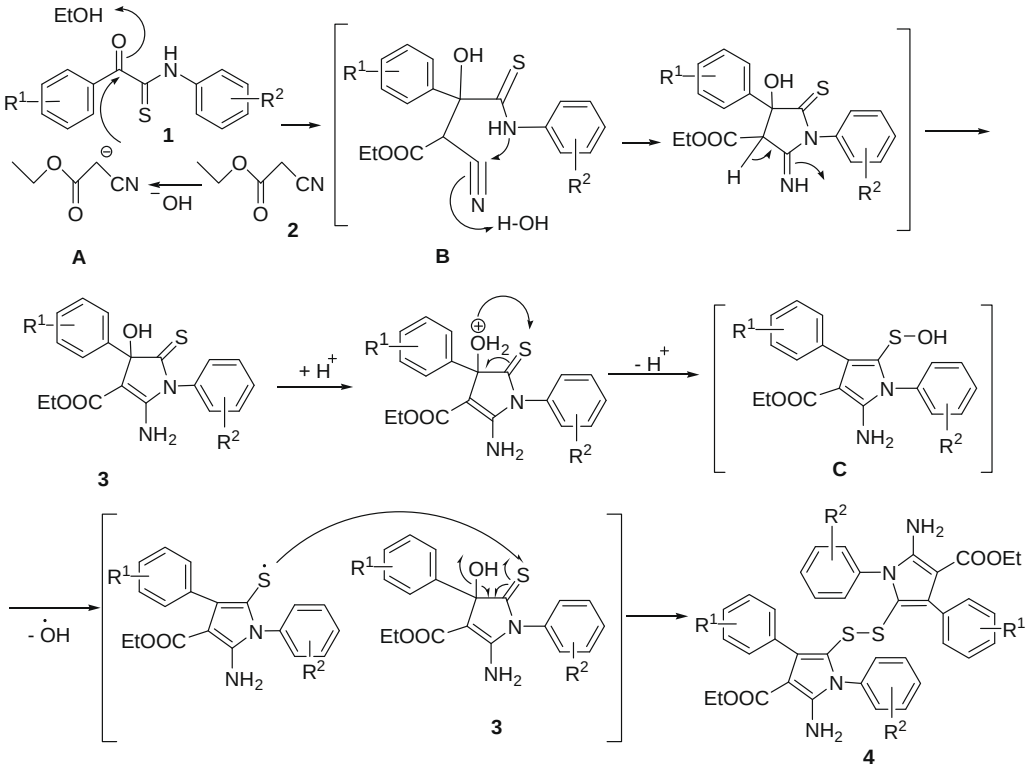

Scheme 2. Possible mechanism for coupling of acyl thioformanilides with ethyl 2-cyanoacetate to disulfides **4**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.020.

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