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Rapid assembly of structurally diverse cyanamides and disulfanes *via* base-mediated aminoalkylation of aryl thiourea†

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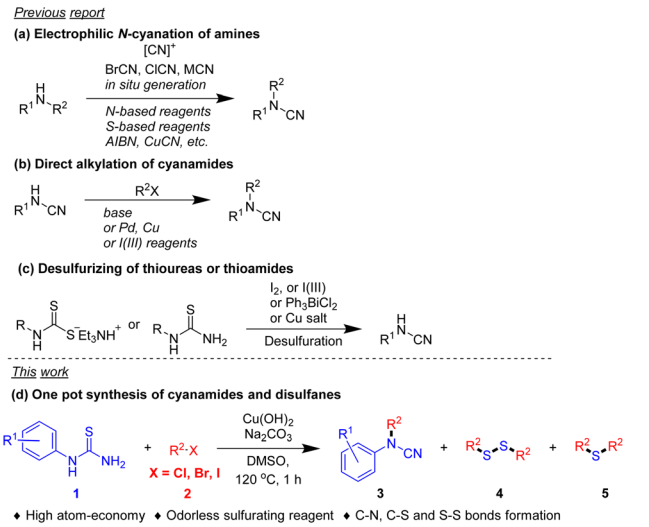
A general method for the preparation of cyanamides and disulfanes from aryl thiourea and halide through a base-mediated strategy is described. Mercaptan and *N*-aryl cyanamide are the key intermediates in the reaction. The current method is convenient, eco-friendly, and has high yields for the synthesis of substituted cyanamide and functional disulfanes in a one-pot procedure from readily available starting materials.

Cyanamide was first discovered as early as 1851 by Cannizzaro, and features a nucleophilic nitrogen atom bearing an electrophilic nitrile unit. Due to their unique structure (N-CN) and chemical properties, cyanamides are valuable organonitrogen compounds in pharmaceuticals, material science, and synthetic applications.[1] Remarkably, cyanamide-containing compounds exhibit interesting biological activities.[2] Moreover, cyanamides are frequently transformed into heterocycles through transition-metal catalyzed cycloaddition reactions.[3] Among cyanamide derivatives, *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) is an efficient cyanation reagent under transition metal catalytic conditions.[2d]

As a valuable dinitrogen resource, many elegant works have been reported for the introduction of a cyanamide group. The most widely known and extensively used strategy for the preparation of substituted cyanamides is based on the electrophilic *N*-cyanation of amines using cyanogen bromide (Scheme 1, Method a). However, BrCN is a very hazardous chemical which can be absorbed into the body by inhalation of its vapor and through the skin and may cause convulsions or death. Several alternative *N*-cyanation procedures have been developed that aim to solve that security issue in recent years.

Kappe and co-workers developed a continuous-flow process for the on-demand generation of BrCN, which subsequent utilization for the construction of cyclic guanidine.[4] The development of safer electrophilic cyanation reagents is another efficient approach. Alcarazo and co-workers introduce two sulfur-based reagents for the efficient electrophilic cyanation.[5] In addition, AIBN[6] and CuCN[7] also serve as sources of nitrile under copper catalysis. The direct nucleophilic substitution of cyanamide is another straightforward method for the synthesis of substituted cyanamides (Scheme 1, Method b).[8] Yet these transformations suffer from uncommon cyanamide sources. In recent years, representative methods for the preparation of substituted cyanamide that do not need a cyanide source have been developed (Scheme 1, Method c). I(III) reagents or iodine-mediated desulfurization of thioamide or dithiocarbamate are the most useful methods to obtain N-substituted cyanamides.[9] Further, transition metal-catalyzed desulphurization is also an efficient method for the synthesis of cyanamides.[10] It is a pity that sulfphur was abandoned in this progress. However, most of



Scheme 1 Synthetic methods for the preparation of cyanamides.

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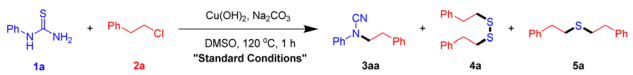
these transformations suffer from certain limitations, such as the need for excessive amounts of waste generating agents, harsh reaction conditions, poor functional group tolerance, and tedious synthetic procedures to access substrates. Hence, there is a high demand for efficient and environmentally benign new methods for the synthesis of cyanamide from readily available starting materials under mild conditions. As part of our continuing studies on green chemistry,[11] we envisage that the sulfphur in thiourea could transfer to useful compounds in elegant reactions. We herein report an efficient method for the synthesis of cyanamides and disulfanes from aryl thiourea and halides in one pot procedure.

Initially, 1-phenylthiourea (**1a**) and (2-chloroethyl)benzene (**2a**) were selected as the model substrates to screen the optimal reaction conditions, and the results are summarized in Table 1. To our delight, under the combination of Na_2CO_3 and $Cu(OH)_2$ in DMSO in the open air at 120 °C for 1 h, the desired product *N*-phenethyl-*N*-phenylcyanamide (**3aa**) and disulfane (**4a**) were obtained in 95% and 79% yield, respectively (Table 1, entry 1). The yields of compounds **3** and **4** were calculated based on arylthiourea (**1**). In addition, thioether (**5a**) was also detected in trace amount by GC-MS. The reaction fails without base (entry 2), and the starting materials **1a** and **2a** were all recoved in yield >95%, showing that base is critical to the reaction. In this reaction, inorganic bases may be acid scavenger, promoting the nucleaddition reaction between aylthiourea and halide. The yield of cyanamide (**3aa**) was increased as the amount of base used in the reaction, however, the yield of disulfane was low without $Cu(OH)_2$ (entries 3–6). Various kinds of bases were then screened, such as K_2CO_3, Cs_2CO_3, $KHCO_3$, $NaHCO_3$, and Et_3N; among them, K salts gave the similar results to Na salts, but no desired products were determined under organic bases (entries 7–11). These results indicated that Na_2CO_3 is the best choice to promote the reaction. With the increase of $Cu(OH)_2$, the yield of disulfane decreased, while the yield of cyanamide remained excellent (entries 12; see ESI† for details). These results may be due to the chelation between copper and mercaptan. Subsequently, different solvents, including water, MeCN, DMF, DMA, acetone, and toluene were estimated, and DMSO was superior to the others (entries 15–18). Furthermore, the reaction temperature and time were also optimized. It was found that increasing the temperature higher than 80 °C can obviously shorten the reaction time, and the reaction finished under 120 °C within 1 h (for more details, see ESI†).

With the optimal reaction conditions in hand, we then tried to explore the generality and limitations of the protocol. First, various halides were investigated and the results are summarized in Table 2. Long-chain chloroalkanes are good substrates for the preparation of corresponding cyanamides (**3ad–3ae**) in 84% to 95% yields and disulfanes (**4d–4e**) in 73% to 95% yields. Phenol ether is tolerant in the reaction, and the corresponding cyanamide (**3af**) and disulfane (**4f**) were obtained in high yields. Simple primary chloroalkane and steric-hindrance halides can also offer corresponding products (**3ag**, **3ah**) in 70% and 88% yields, respectively. Benzyl chloride and its alkyl, alkoxy, halo, and cyan substituted derivatives will react smoothly and produce cyanamides (**3ai–3aq**) in moderate to good yields. To our surprise, except for 3-methylbenzyl chloride affording

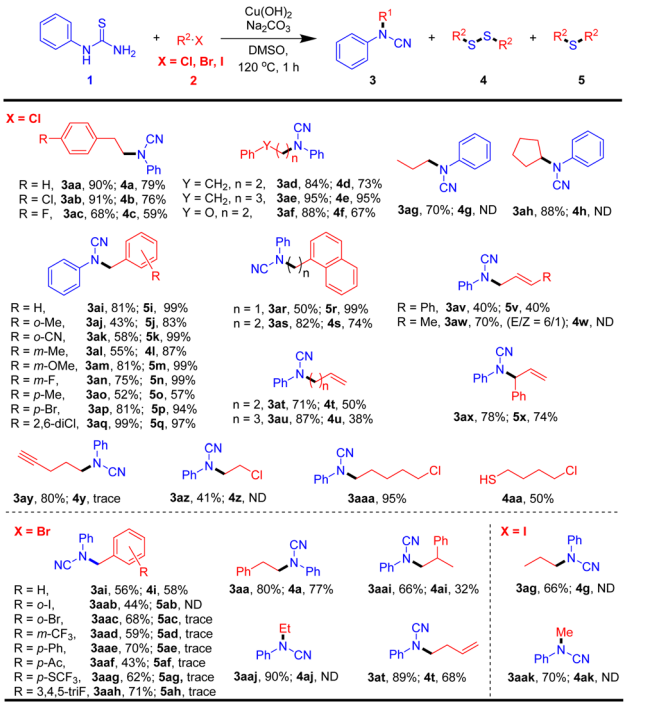
Table 1 Optimization of reaction conditions[a]



Entry	Base	Solvent	Yield of **3aa**[b]/%	Yield of **4a**[b]/%	Yield of **5a**[b]/%
1	Na_2CO_3	DMSO	95 (93)	79 (70)	Trace
2	—	DMSO	0	0	0
3[c,d]	Na_2CO_3	DMSO	33	16	20
4[c,e]	Na_2CO_3	DMSO	65	30	32
5[c,f]	Na_2CO_3	DMSO	74	26	30
6[c,g]	Na_2CO_3	DMSO	81	26	40
7	K_2CO_3	DMSO	97	70	Trace
8	Cs_2CO_3	DMSO	70	50	Trace
9	$NaHCO_3$	DMSO	90	75	Trace
10	$KHCO_3$	DMSO	92	70	Trace
11	Et_3N	DMSO	0	0	0
12[h]	Na_2CO_3	DMSO	97	0	0
13[i]	Na_2CO_3	DMSO	81	57	Trace
14[j]	Na_2CO_3	DMSO	92	70	Trace
15[k]	Na_2CO_3	H_2O	0	0	0
16[l]	Na_2CO_3	CH_3CN	76	30	Trace
17	Na_2CO_3	DMAc	79	62	Trace
18	Na_2CO_3	DMF	91	71	Trace

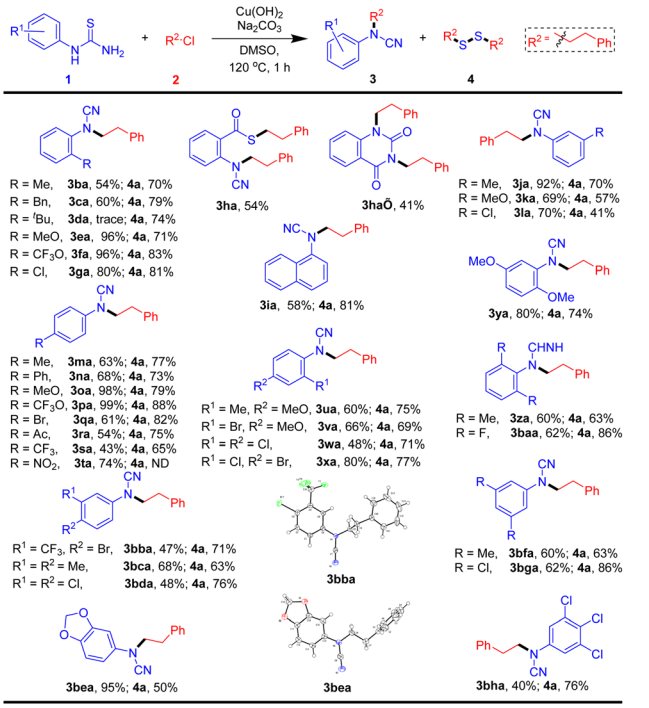
[a] Unless otherwise note, all reactions were performed with **1a** (0.20 mmol), **2a** (0.48 mmol, 2.4 equiv.), base (2.5 equiv.), $Cu(OH)_2$ (10 mol%), solvent (0.5 mL) at 120 °C for 1 h. [b] Yields were based on ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard. The value in parentheses is the isolated yield of product. [c] Without $Cu(OH)_2$. [d] Base (0.5 equiv.). [e] Base (1.0 equiv.). [f] Base (1.5 equiv.). [g] Base (2.0 equiv.). [h] $Cu(OH)_2$ (1.0 equiv.). [i] **2a** (2.0 equiv.). [j] **2a** (2.2 equiv.). [k] At 100 °C for 12 h. [l] At 80 °C for 12 h. DMAc = *N*,*N*-dimethylacetamide.

Table 2 Substrate scope of various halides 2[a]



[a] All reactions were performed with **1a** (0.2 mmol), **2** (2.4 equiv.), $Cu(OH)_2$ (10 mol%), Na_2CO_3 (2.5 equiv.), DMSO (0.5 mL) at 120 °C for 1 h. Yields referred to isolated yield.

Table 3 Substrate scope of various arylthioureas 1[a]

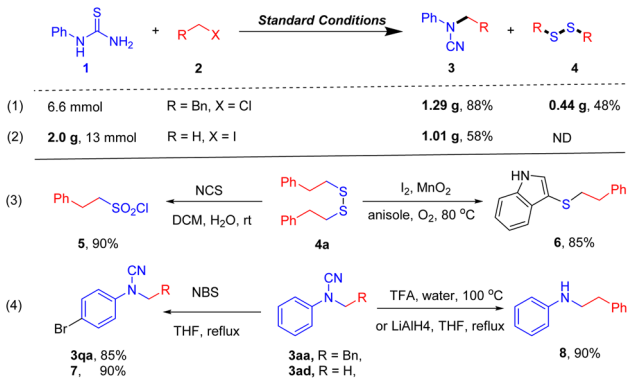


[a] All reactions were performed with **1** (0.2 mmol), **2a** (2.4 equiv.), $Cu(OH)_2$ (10 mol%), Na_2CO_3 (2.5 equiv.), DMSO (0.5 mL) at 120 °C for 1 h. Yields referred to isolated yield.

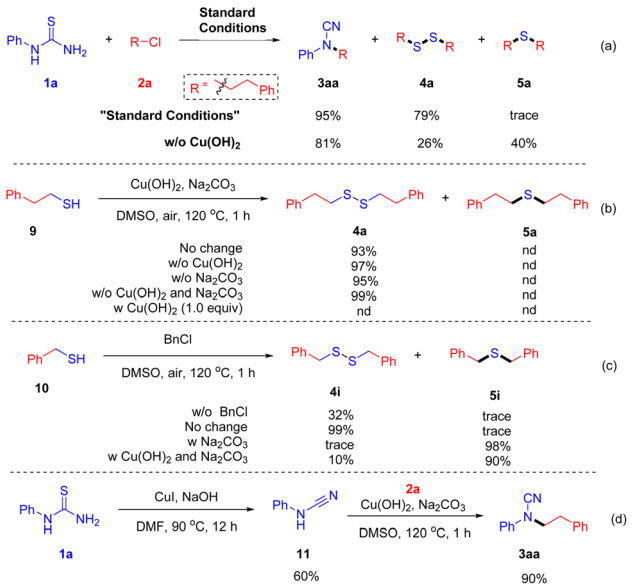
disulfane **4l**, the other benzyl chloride derivatives produce thioethers (**5i–5q**) in excellent yields under standard conditions. Halides with a terminal or internal C=C double bond are suitable partners and give the desired products (**3av–3ax**, **4v–4x**) in moderate yields. Particularly, 5-chloropent-1-yne is also perfectly compatible under this reaction condition, and the corresponding cyanamide (**3ay**) was obtained in an 80% yield. To our delight, dichloroalkanes are acceptable for the preparation of halo-substituted cyanamides (**3az–3aaa**) and halo-substituted disulfane products (**4aa**). Benzyl bromide and its electron-withdrawing or donating derivatives can offer moderate yields of cyanamide products (**3ai**, and **3aab–3aah**). To our confusion, sulfane products were not easily obtained in these cases, and olyl dibenzyldisulfane (**4i**) was obtained in 58% isolated yield. Moreover, bromoethane can produce cyanamide in excellent yield (90%) under standard reaction conditions. Furthermore, 1-iodopropane and methyl iodide successfully provide corresponding products (**3ag** and **3aak**) in yields of 66% and 70%, respectively. These results indicated that chloride, bromide, and iodo hydrocarbons are all available materials for the corresponding cyanamide products.

To explore further the generality of this protocol, various structurally diverse arylthioureas were then evaluated, and the representative results are summarized in Table 3. *Ortho*-substituted phenyl thioureas are tested first. Satisfactorily, both electron-rich (Me, Bn, MeO, and CF_3O) and electron-withdrawing (Cl) substituents arylthioureas can be successfully coupled with **2a**, and the corresponding cyanamide products **3ba–3ga** and disulfane **4a** were furnished in yields ranging from 54% to 96%. However, the high-steric-hindrance substrate 1-(2-(*tert*-butyl)phenyl)thiourea cannot obtain a cyanamide product. In addition, ethyl 2-thioureidobenzoate reacting with **2a** will produce **3ha** and **3ha′** in moderate yields. In this case, **3ha** was generated *via* thiolysis between ethyl ester and *in situ* disulfane **4a**. Similarly, naphthyl thiourea substrate gives the corresponding cyanamide **3ia** in 58% yield and disulfane **4a** in 81% yield. *Meta*-substituted phenyl thioureas were well tolerated under the current reaction conditions, and the cyanamide products **3ja–3la** were obtained in good to excellent yields. Either electron-donating or electron-withdrawing substituents on the *para* site, aryl thioureas are successful in achieving the desired products. To our delight, multi-substituted alkyl, alkoxyl, and/or halogen on the phenyl ring were well accommodated, and the corresponding products were generated in yields ranging from 48 to 95%. The configurations of **3bba** (ref. 12) and **3bea** (ref. 13) were unequivocally confirmed by X-ray crystallographic analysis.

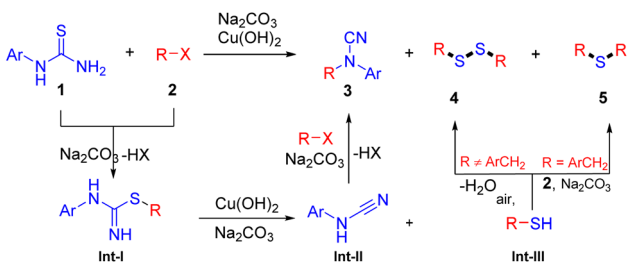
To investigate the practicality of this method, gram-scale reactions and further transformations were carried out (Scheme 2). On a 6.6 mmol scale, the desired cyanamide **3aa** and disulfane **4a** were isolated in 88% and 48% yield, respectively. It is noteworthy that this approach can perform at a 2 g scale with iodomethane for the synthesis of the desired methyl cyanamide product (**3aak**) in 58% yield. Subsequently, disulfane



Scheme 2 Scale-up reactions and application transformations of products.



Scheme 3 Control experiments (a–d).



Scheme 4 Plausible mechanism.

4a can be readily converted to the corresponding sulfonyl chloride **5** and sulfenylindole **6** (ref. 14) in high yield. These results show that disulfane can replace mercaptan as an odorless reagent in organic synthetics. Phenyl cyanamides were easily brominated in the para site of the phenyl ring when treated with NBS in THF under reflux. It is a pity that the cyan group was eliminated when treating with TFA or $LiAlH_4$.

In order to further understand the reaction mechanism, some control experiments (Scheme 3) were conducted. First, the model reaction is performed under standard conditions (eqn (a)). Cyanamide (**3a**) and disulfane (**4a**) were found in the yields of 95% and 79%, respectively, and only a trace amount of thioether (**5a**) was detected by GC-MS. In the absence of $Cu(OH)_2$, the yield of thioether (**5a**) increased dramatically. Meanwhile, trace amounts of thiol and *N*-phenyl cyanamide were detected in GC-MS. These results showed that $Cu(OH)_2$ may promote the formation of disulfane (**4a**). Subsequently, 2-phenylethanethiol (**9**) was tested under various conditions (eqn (b)), and only disulfane (**4a**) was obtained. In the presence of 1.0 equiv. $Cu(OH)_2$, thiol (**9**) is consumed, and no sulfane products are detected by GC-MS. Indicating that excess copper salt may chelate with mercaptan. Moreover, 1,2-dibenzyldisulfane (**4i**) is produced in high yield when benzyl mercaptan (**10**) is performed under air in the presence or absence of benzyl chloride (eqn (c)). However, thiother (**5i**) becomes the main product in the presence of a base. Indicating that base facilitates the S_N2 reaction between thiol and halide. Furthermore, substituted cyanamide (**3aa**) was obtained successfully when treating *N*-phenyl cyanamide (**11**) with **2a** under standard conditions. These results indicated that mercaptan and *N*-phenyl cyanamide might be the intermediates in the reaction (Scheme 4).

Based on the above experimental results and previous reports,[15] a tentative mechanistic interpretation of the preceding observations is proposed in Scheme 4. First, base-promoted nucleoaddition of halide to arylthiourea forms isthiourea **Int-I**, which undergoes further intramolecular elimination in the presence of base and copper to generate cyanamide **Int-II** and thiol intermediate **Int-III**. Then halide **2** and **Int-II** undergo S_N2 progress to afford the substituted cyanamide product (**3**). Meanwhile, thiol **Int-III** is oxidized by air to form a sulfane compound.

Conclusions

In summary, a simple method for the preparation of cyanamides and disulfanes has been established under mild reaction conditions in one pot. Many diverse substituted cyanamides and functional sulfanes are successfully prepared in moderate to excellent yields with this strategy. Importantly, the present methodology demonstrates excellent functional group compatibility, high atom- and step-economy, and mild reaction conditions. Further studies on the synthetic application of this strategy are underway in our lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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