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Synthetic Methods

General and Practical Formation of Thiocyanates from Thiols

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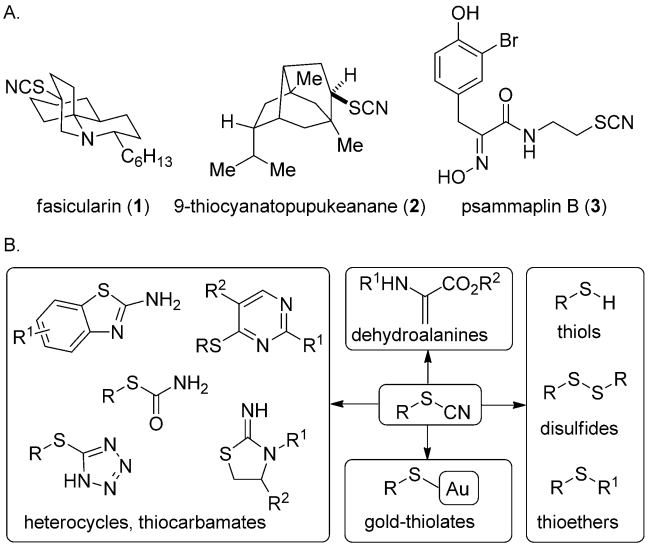
Abstract: A new method for the cyanation of thiols and disulfides using cyanobenziodoxol(on)e hypervalent iodine reagents is described. Both aliphatic and aromatic thiocyanates can be accessed in good yields in a few minutes at room temperature starting from a broad range of thiols with high chemioselectivity. The complete conversion of disulfides to thiocyanates was also possible. Preliminary computational studies indicated a low energy concerted transition state for the cyanation of the thiolate anion or radical. The developed thiocyanate synthesis has broad potential for various applications in synthetic chemistry, chemical biology and materials science.

Introduction

Heteroatom-containing functional groups are essential in synthetic and medicinal chemistry, as they have a tremendous influence on the physical and biological properties of molecules and serve as a platform for functionalization. Thiocyanates, in particular, have attracted broad attention. They can be found in bioactive natural products, such as fasicularin (**1**),[1a,b] 9-thiocyanatopupukeanane (**2**)[1c] and psammaplin B (**3**)[1d] (Scheme 1 A). Thiocyanates are also very important precursors in synthetic and medicinal chemistry, chemical biology and materials science (Scheme 1 B). They can be converted easily to thiocarbamates and structurally diverse heterocycles.[2] The good leaving group ability of the cyanide group makes them mild electrophilic sulfur-transfer reagents to access disulfides and thioethers.[3a–e] Thiocyanates can also easily be converted into thiols, and the cyano group is consequently a useful and atom-economical protecting group for sulfur.[3f,g] Furthermore, thiocyanates derived from cysteine are also important intermediates to access dehydroalanines under mild conditions, to promote cleavage of the amide bonds in peptides and proteins and to study the mechanism of enzymes with vibrational spectroscopy.[4] Finally, thiocyanates are highly useful precursors for the synthesis of gold-thiolate nanoparticules.[5] Traditionally, this functional group has been introduced by nucleophilic or electrophilic thiocyanation of organic molecules, and their accessibility has been limited by the availability and reactivity of the required precursors.[2a] Other disconnections giving access to thiocyanates would be highly desirable.



Scheme 1. Thiocyanates in: A) natural products, and B) as synthetic precursors.

The synthesis of thiocyanates from thiols would constitute such an alternative disconnection, especially in light of the broad range of commercial or easily accessible thiols. This can be achieved either by nucleophilic cyanation of an activated thiol derivative[6] or direct electrophilic cyanation of the thiol using reagents such as **4**–**9** (Scheme 2 A).[4,7] The latter route is more efficient, as it can be carried out in a single step. Nevertheless, no truly general method for the selective cyanation of both aliphatic and aromatic thiols has been reported and the frequently used electrophilic cyanation reagent, cyanogen bromide (**4**), is toxic, difficult to manipulate and highly reactive, which leads to side reactions. Consequently, the discovery of new electrophilic cyanation reagents is an intensive topic of research.[8]

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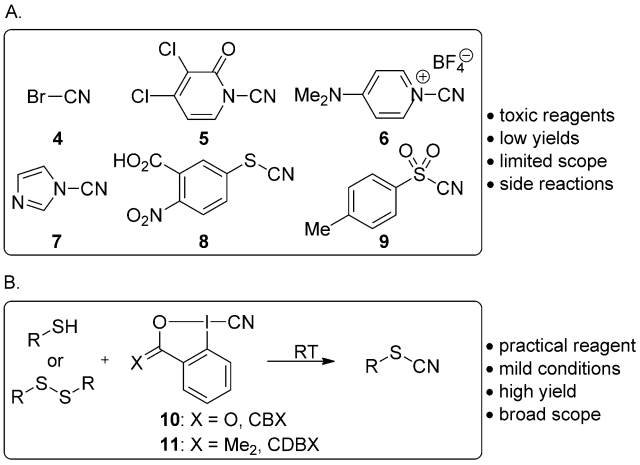


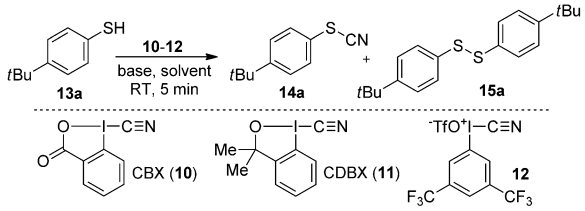
Scheme 2. A) Previously reported reagents for thiol cyanation, and B) our new approach.

To develop new electrophilic cyanation methods, the use of hypervalent iodine reagents is highly promising, due to the exceptional reactivity of three-center four-electron bonds.[9] Nevertheless, hypervalent iodine compounds are also strong oxidants, which limits their use for the functionalization of thiols due to the easy formation of disulfides by oxidative dimerization. Recently, the use of cyclic hypervalent iodine reagents, especially benziodoxol(on)es, has led to important breakthroughs in atom-transfer reactions.[10] In the field of thiol functionalization in particular, Togni and co-workers reported the first example of trifluoromethylation,[11] whereas our group developed a practical alkynylation of thiols using ethynylbenziodoxolone (EBX) reagents.[12] However, to the best of our knowledge, hypervalent iodine reagents have never been used for the synthesis of thiocyanates starting from thiols. Herein, we report the first use of 1-cyano-1,2-benziodoxol-3-(1*H*)-one (CBX, **10**) and 1-cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxol (CDBX, **11**),[9d] for the cyanation of thiols (Scheme 2B). The reaction proceeded at room temperature in a few minutes in nearly quantitative yields for a broad range of aromatic and aliphatic thiols and displayed unprecedented functional group tolerance. CBX reagents could also be used for accessing thiocyanates from disulfides in up to 92% yield. In addition, a combined experimental and computational investigation gave a first insight into the reaction mechanism.

Results and Discussion

We started our study with simple commercially available thiophenol **13a** as a model substrate (Table 1). With 1-cyano-1,2-benziodoxol-3(1*H*)-one (CBX, **10**), we found that the desired thiocyanate **14a** could be obtained in moderate yield using triethylamine as a base (entry 1). The choice of the base was crucial to obtain good yields of the thiocyanate product **14a** and minimize formation of the undesired disulfide **15a** arising from the oxidative dimerization of thiophenol **13a** (entries 1–4). Stronger bases such as tetramethylguanidine (TMG), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to the desired thiocyanate **14a** as the main product (entries 2–4). Among the latter, DBU showed the best result with a yield above 95% (entry 4). In the absence of base, disulfide **15a** was obtained as the major product (entry 5). An important effect of the solvent was also apparent, as significant formation of disulfide **15a** was observed in other solvents (entries 6 and 7). 1-Cyano-3,3-dimethyl-1,2-benziodoxole (CDBX, **11**), also gave an excellent result (entry 8). The cyclic hypervalent iodine regents **10** and **11** were superior to iodonium salts such as **12**,[9j] which led to the formation of disulfide **15a** as major product (entry 9).

Table 1. Optimization of thiocyanate formation.[a]

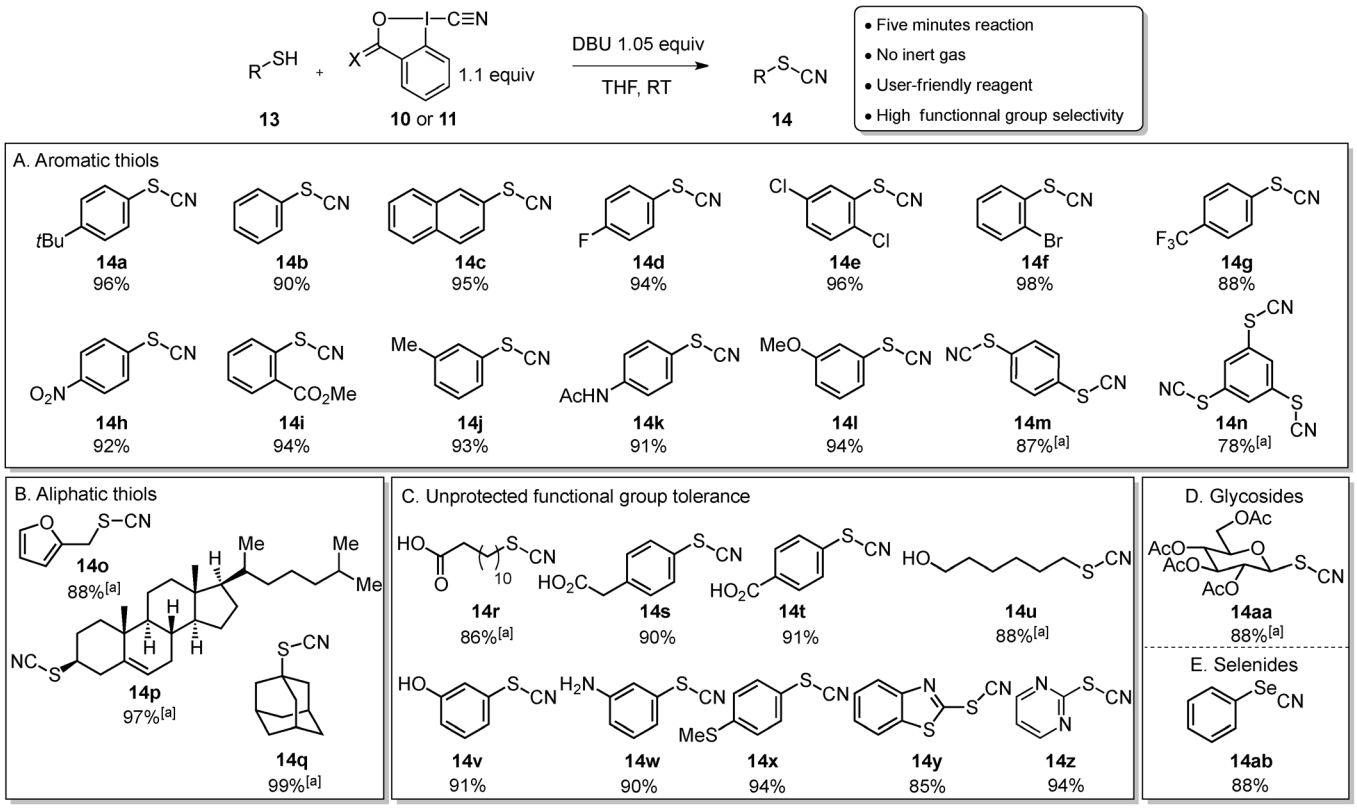


Entry	10–12	Base	Solvent	Yield 14a[b] [%]	Yield 15a[b] [%]
1	**10**	Et_3N	THF	40	60
2	**10**	TMG	THF	79	20
3	**10**	TBD	THF	74	26
4	**10**	DBU	THF	>95	<5
5	**10**	–	THF	<10	90
6	**10**	DBU	MeOH	64	35
7	**10**	DBU	CH_3CN	86	12
8	**11**	DBU	THF	>95	<5
9	**12**	DBU	THF	17	81

[a] 4-*tert*-Butylthiophenol (**13a**, 0.50 mmol), cyanide transfer reagent (**10**–**12**, 0.550 mmol), base (0.525 mmol), solvent (5.0 mL), 23 °C, 5 min, open flask. [b] Isolated yield of spectroscopically pure product.

Under the optimized conditions CBX (**10**) or CDBX (**11**; 1.1 equiv) was added in one portion to a solution of the thiol **13a** (1.0 equiv) and DBU (1.05 equiv) in THF at room temperature and stirred for five minutes in an open-air flask to give the thiocyanate **14a** in 96% isolated yield (Scheme 3A). The cyanation of thiophenol (**13b**) and 2-thionaphthalene (**13c**) gave the corresponding products **14b** and **14c** in 90 and 95%, respectively. Both electron-withdrawing (products **14d–i**) or electron-donating (products **14j–l**) groups were well tolerated and gave thiocyanates in 88–98% yield. The cyanation was successful in the presence of numerous functional groups such as halogens (fluorides, chlorides and bromides), nitro groups, esters, amides and ethers. Double and triple cyanation reactions were also possible, as demonstrated by the synthesis of bisthiocyanate **14m** and tristhiocyanate **14n** in 87 and 78%, respectively. These compounds are particularly interesting scaffolds for materials science as a platform for dendrimeric heterocycle synthesis.[2a,7b,13]

There are only a few methods for the efficient conversion of aliphatic thiols to the corresponding thiocyanates under mild conditions.[7c,14] The use of cyanation reagent **10** allowed us to



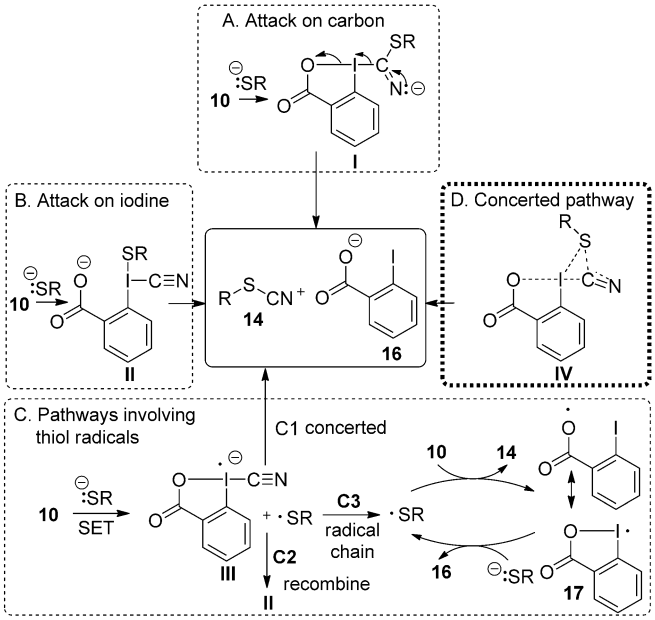
Scheme 3. General and practical thiocyanate synthesis from various thiols. The reaction conditions of Table 1, entry 8 with reagent **11** were used. [a] Reagent **10** was used (conditions of Table 1, entry 4).

selectively convert primary, secondary and tertiary aliphatic thiols into thiocyanates in a general and practical fashion (Scheme 3B, products **14o–q**). In particular, the more complex steroid **14p** was obtained in an excellent 97% yield.

Chemoselectivity is the main challenge for cyanation reactions as acidic or nucleophilic functionalities can react with electrophilic cyanation reagents and consequently need to be protected, adding extra steps to the synthetic sequence. In particular, free amines and anilines are known to be efficiently cyanated with electrophilic cyanation reagents.[7e] To our delight, the cyanation reaction could be selectively carried out in the presence of unprotected aliphatic (products **14r** and **14s**) and aromatic (product **14t**) carboxylic acids in 86–91% yield (Scheme 3C). With a free aliphatic alcohol and a phenol, the thiocyanates **14u** and **14v** were obtained in 88 and 91%, respectively. In the case of aniline **13w**, the cyanation was completely selective for sulfur and **14w** was obtained in 90% yield. This result points to the superior selectivity of hypervalent-iodine-based reagents and their strong affinity for sulfur. On the other hand, it was possible to selectively cyanate a thiol in the presence of a thioether to obtain thiocyanate **14x** in 94% yield. The methodology was extended to the use of heterocyclic substrates giving thiocyano-benzothiazole **14y** or thiocyano-pyrimidine **14z** in 85 and 94% yield, respectively. Heterocyclic thiocyanates are useful building blocks for the synthesis of bioactive compounds.[15] Thiocyano-glycosides are known to be very good glycoside donors in glycosylation reactions, especially for 1,2-*cis*-glycosylation.[16] Under our optimized conditions, tetra-acetyl-β-thioglucose **13aa** cleanly gave the desired thiocyanate **14aa** in 88% yield without epimerization to the α form (Scheme 3D). Finally, phenylselenol (**13ab**) was found to be a suitable substrate for this reaction and selenocyanate **14ab** could be obtained in 88% yield (Scheme 3E).

Several pathways can be proposed for the reaction mechanism (Scheme 4).[9] A first possibility would be nucleophilic attack on the carbon of the cyanide group to form thioimidate **I** (pathway A). 1,2-Elimination would then give thiocyanate **14** and benzoate **16**. However, this mechanism is less probable when considering that the most electrophilic position is usually on the iodine for this type of reagents.[9] Therefore, attack on the iodine atom appears more probable to give intermediate **II** upon ring opening of the benziodoxolone heterocycle (pathway B). Reductive elimination on iodine would then lead to thiocyanate **14**. This type of mechanism has indeed often been proposed for the functionalization of nucleophiles with hypervalent iodine reagents.[9]

Nevertheless, when considering the strong oxidizing properties of hypervalent iodine reagents, mechanisms involving a single electron transfer and the subsequent formation of radical intermediates also constitute an important alternative (pathway C). In the case of related benziodoxolone reagents for trifluoromethylation, the formation of a trifluoromethyl radical has often been proposed.[11] However, when considering the much lower stability of the cyano radical, such an inter-



Scheme 4. Speculative mechanism pathways for the cyanation reaction.

mediate appears highly improbable.[17] In contrast, a single electron transfer between reagent **10** and a thiolate anion could be possible, although Lewis or Brønsted acid activation of hypervalent iodine reagents is usually needed to promote single electron transfer.[18] Several pathways could then be considered for further reaction of the formed radical anion **III** and the thiol radical: 1) concerted reaction to directly give the thiocyanate (pathway C1), 2) radical recombination to give intermediate **II** followed by reductive elimination (pathway C2), or initiation of a radical chain reaction starting with attack of the thiol radical onto reagent **10** (pathway C3). In the latter case, the formed benziodoxole radical **17** would be further reduced by a thiolate anion to give benzoate **16** and regenerate a thiol radical. If the reaction would occur via pathway C3, it should be possible to intercept the formed thiol radicals with trapping reagents. However, no adduct could be observed in the presence of phenylacetylene and 1,1-dicyclopropylethene, which are known to react very quickly with thiol radicals.[19] Consequently, this pathway also appears less probable.

Finally, a last alternative would involve a concerted mechanism via a three-atom transition state **IV** (pathway D, Scheme 4). Although this alternative has not yet been proposed in the literature for the cyanation of thiols, we have recently discovered by computation that such a transition state is possible in the case of the related alkynylation reaction.[20] We consequently turned to computational chemistry to investigate this intriguing mechanism pathway.

Computations (at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP or M06-2X/def2-TZVP//M06-2X/def2-SVP theoretical level, see computational details section) designed to probe the potential energy surface with phenyl thiolate **13b′** allowed us to identify low-energy van der Waals complexes **V** indeed indicating a significant interaction between the sulfur and the iodine atom (Figure 1). Nevertheless, the sulfur atom is already shifted towards the carbon of the cyanide group (S–I and S–C lengths of 2.895 and 3.206 Å, respectively). Starting from **V**, no stable intermediate corresponding to either thioimidate **I** or intermediate **II** containing a formal S–I bond was observed. Instead, a low energy (8.8 kcal mol^{-1}) transition state **IV** led directly to thiocyanate **14b** and iodobenzoate **23** (complex **VI**).[21,22] This energetically favorable concerted pathway is in accordance with the high reaction rate. As observed for the alkynylation of thiols,[20] the linear geometry at the cyanide carbon was distorted and a significant transfer of negative charge on the nitrogen atom was observed (−0.46 computed Hirshfeld iterative charge). The higher electronegativity of the nitrogen atom could further stabilize the formed charge and lower the energy of the transition state.

In addition to thiophenolate (**13b′**), thiophenol radical (**13b″**) and thiophenol (**13b**) itself could also lead to thiocyanate formation. Consequently, the energies and geometries for van der Waals complex **V** and transition state **IV** were computed for these two molecules. Interestingly, the addition of thio-

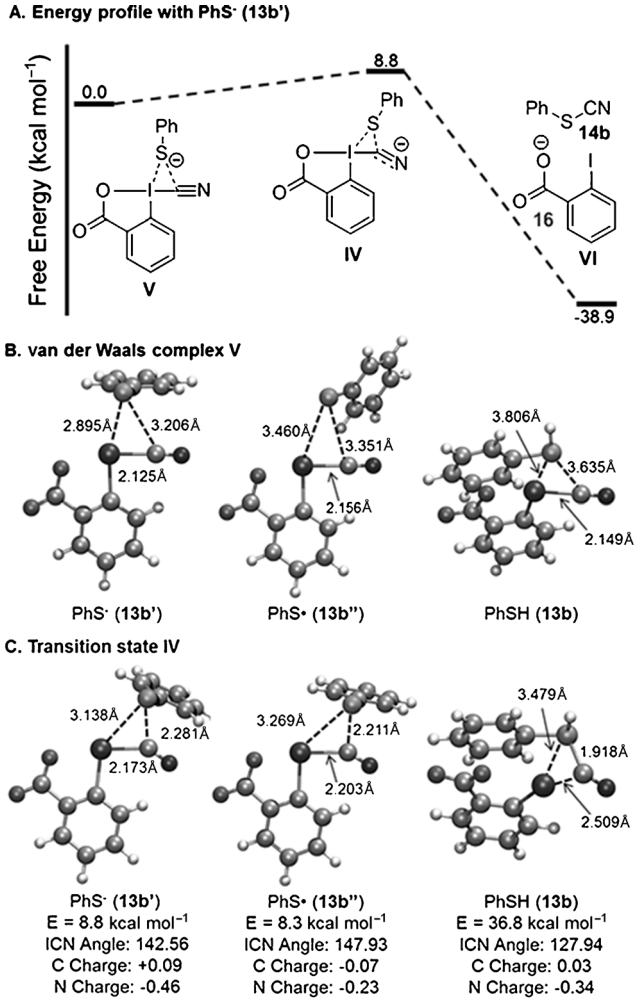


Figure 1. Free-energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the cyanation of thiophenolate (**13b′**) with CBX (**10**) and computed geometries (M06-2X/def2-SVP level) for van der Waals complex **V** and transition state **IV** with thiophenolate (**13b′**), thiophenol radical (**13b″**) and thiophenol (**13b**).[21]

phenol radical **13b**'' was also a very facile process, with a transition state energy of only 8.3 kcal mol^{-1}. The geometries of van der Waals complexes **V** and transition state **IV** are similar to those obtained with thiophenolate **13b**', except that the distance between the sulfur and the iodine atom was significantly longer in complex **V** (3.460 vs. 2.895 Å). It is known that the *para* position to the aryl ring is strongly Lewis acidic in hypervalent iodine reagents,[9] and a stronger interaction with the nucleophilic thiolate compared to the neutral radical could be reasonably expected. In contrast, a completely different result was obtained using thiophenol (**13b**) itself as nucleophile: a much higher transition-state energy (36.8 kcal mol^{-1}) was observed, as well as a nearly complete change of the geometry to trigonal planar (ICN angle of 128°). Consequently, direct reaction of the neutral thiol appears highly improbable, and it is in good agreement with the lack of thiocyanate formation in the absence of base (Table 1, entry 5).

Finally, the energy profile and the computed geometries were also computed in the case of the reaction of CDBX (**11**) with thiophenolate (**13b**'; Figure 2).

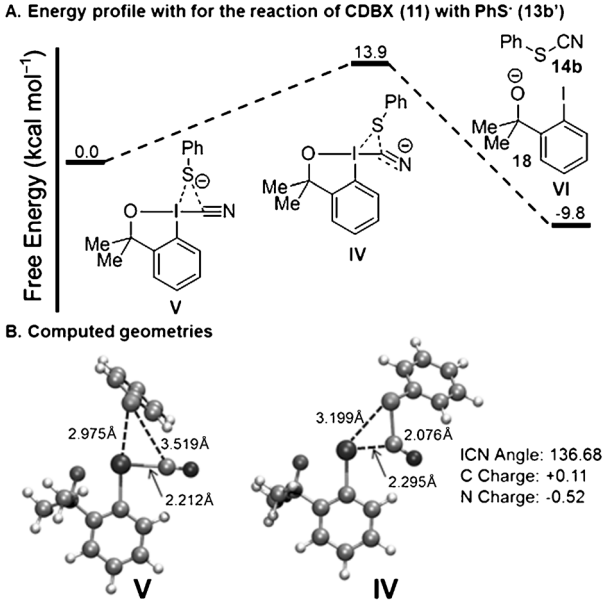
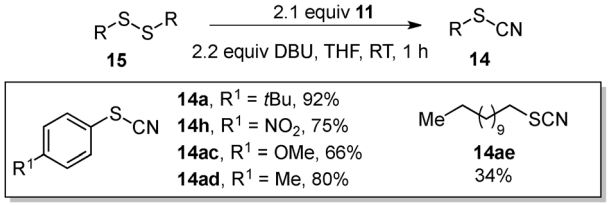


Figure 2. Free-energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the cyanation of thiophenolate (**13b**') with CDBX (**11**) and computed geometries (M06-2X/def2-SVP level) for van der Waals complex **V** and transition state **IV**.[23]

A similar profile was obtained, although transition state **IV** was higher in energy (13.9 vs. 8.8 kcal mol^{-1} with CBX (**10**)). Concerning the geometries, a stronger distortion from linearity was observed (ICN angle of 137° vs. 143°) and the C–I length was larger (2.295 vs. 2.173 Å) and the C–S distance shorter (2.076 vs. 2.281 Å), corresponding to a later transition state.

During optimization of the reaction conditions with thiolate **13a**, the formation of disulfide **15a** could be avoided by the right choice of reagent, base and solvent. However, even under the optimized conditions, formation of small amounts of disulfide **15a** was still observed by TLC in the first minute of reaction, but gradually disappeared afterwards. We consequently wondered if disulfide **15a** could also be converted into the desired thiocyanate **14a** under the reaction conditions. Indeed, when **15a** was treated with 2.1 equivalents of CDBX (**11**), thiocyanate **14a** was obtained in 92% yield in one hour (Scheme 5). To the best of our knowledge, this constitutes the first report of efficient transformation of a disulfide into a thiocyanate, as most reported methods can reach a maximum of only 50% yield.[6,24] Under the same reaction conditions, thiocyanates **14h** and **14ac–d** bearing either electron-withdrawing or electron-donating groups could be obtained in 66–80% yield. The cyanation of an aliphatic disulfide was also possible, but thiocyanate **14ae** was obtained in lower yield (34%).



Scheme 5. Thiocyanate formation from disulfides.

Conclusions

In conclusion, we have developed a very general and practical methodology to access useful thiocyanates from readily available thiols and disulfides. This methodology utilizes the easily accessible and user-friendly benziodoxoles CBX (**10**) and CDBX (**11**) as electrophilic cyanation reagents. The mild reaction conditions and high chemoselectivity allowed us to successfully prepare aromatic-, benzylic-, and aliphatic thiocyanates, as well as thiocyano-saccharides or thiocyano-steroids. The methodology shows an unprecedented functional-group tolerance towards carboxylic acids, alcohols, thioethers and anilines. The high rate and selectivity observed could be tentatively rationalized by a low energy barrier concerted mechanism available to thiolates and thiol radicals as nucleophiles. All attempted trapping experiments for thiol radicals were unsuccessful to date. Nevertheless, the presence of short-lived radical intermediates cannot be excluded without further investigations. The thiol-cyanation reaction we have developed has the potential to become a reference method for thiocyanate formation from thiols and disulfides with various applications in synthetic chemistry, chemical biology and materials science.

Experimental Section

Computational details[25]

Geometries were optimized using Truhlar's M06–2X[26] density functional with the def2-SVP basis set in Gaussian 09.[27] M06-2X computations employed the "Ultrafine" grid to remove known problems with the size of the integration grid for this functional family.[28] To obtain refined energy estimations that explicitly account for nonbonded interactions, a density dependent dispersion correction (-dDsC)[29] was used, appended to the PBE0[30] functional

(PBE0-dDsC). PBE0-dDsC single-point computations made use of the slater-type orbital 3-ζ basis set, TZ2P, as implemented in ADF.[31] To confirm the accuracy of the PBE0-dDsC computations, a second set of single-point energies was obtained at the M06-2X/def2-TZVP level. All reported free energies include the effects of solvation (in THF) using the implicit continuum model for realistic solvents[32] (COSMO-RS), also as implemented in ADF, as well as free energy correction derived from M06-2X/def2-SVP computations. Iterative Hirshfeld charges[33] were computed using Q-Chem.[34]

Experimental procedures

Caution! Hypervalent iodine reagents are high-energy compounds which should be used with appropriate care. Compounds **10** and **11** are stable at room temperature, but show a strong exothermic decomposition at 151 and 133 °C, respectively, by DSC measurement. We recommend not using these reagents above 40 °C and running reactions behind a protective shield. An advantage of the method is to avoid the use of highly toxic cyanide anions. Nevertheless, as the formation of small amounts of cyanide cannot be excluded, all relevant measures have to be taken when performing the cyanation step.[35] In particular, the aqueous layers were basified and disposed separately. All open-flask reactions were set up in well ventilated fume-hoods.

General procedure for the cyanation of thiols

A 25 mL round-bottom flask was charged with a magnetic stirring bar, thiol derivative (0.500 mmol, 1.00 equiv) and THF (5.0 mL). To this solution was added 1,8-diazabicycloundec-7-ene (DBU, 79.0 μL, 0.525 mmol, 1.05 equiv), followed by 1-cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole (CDBX (**11**), 158 mg, 0.550 mmol, 1.10 equiv) or 1-cyano-1,2-benziodoxol-3-(1*H*)-one (CBX (**10**), 150 mg, 0.550 mmol, 1.10 equiv). In case DBU addition yielded a THF-insoluble thiolate, CDBX or CBX was added prior to DBU. An additional equivalent of DBU (total amount: 153 μL, 1.03 mmol. 2.05 equiv) was added for carboxylic acid containing substrates. The resulting reaction mixture was stirred in an open flask for 5 min at room temperature (unless otherwise stated). The reaction was quenched with 5% aq. citric acid (10 mL). The aq. mixture was extracted with EtOAc (3× 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated, in vacuo. The crude product was further purified by column chromatography.

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Keywords: chemoselectivity · cyanation · hypervalent iodine · thiocyanates · synthetic methods

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[22] Examination of the intrinsic reaction coordinate (IRC) further supported the concerted nature of the proposed mechanism. See the Supporting Information for selected IRC structures.

[23] Electronic energies obtained with M06-2X/def2-TZVP: 17.9 kcal mol^{-1}. See the Supporting Information for further details.

[24] At this stage, the exact mechanism of the conversion of disulfides to thiocyanates is unknown and will be the topic of future studies.

[25] The same computational methods were used as in ref. [20], consequently the technical section is reprinted (adapted) with permission from *J. Am. Chem. Soc.* **2014**, *136*, 16563, copyright 2014 American Chemical Society.

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FULL PAPER

Synthetic Methods

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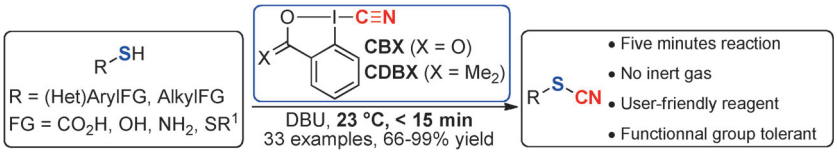
General and Practical Formation of Thiocyanates from Thiols



Easy and general: A new method for the cyanation of thiols using cyanobenziodoxol(on)e hypervalent iodine reagents is described. Both aliphatic and aromatic thiocyanates can be accessed in good yields in a few minutes at room temperature with high chemioselectivity. The developed thiol-cyanation reaction has broad potential for the formation of thiocyanates with various applications in synthetic chemistry, chemical biology and materials science.