Formation of 1,10-Disubstituted Benzo[*c*]cinnolines. Synthesis and Molecular Structure of 1-Amino-10-propylthiobenzo[*c*]cinnoline and Cyclization to 4-Propylcinnolino[5,4,3][*c*,*d*,*e*][1,2]benzothiazine

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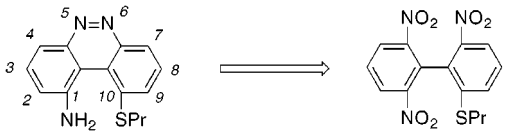
The first 1,10-heterodisubstituted benzo[*c*]cinnoline derivative **1** was prepared from the trinitrobiphenyl **2**. Investigation of the mechanism of ring closure in **2**, **5**, and **8** revealed a complex reduction−oxidation−cyclization sequence. The mechanism is discussed in light of the stereoelectronic demands of the substituent functionalities. Benzo[*c*]cinnoline derivative **1** [$C_{15}H_{15}N_3S$, monoclinic, $P2_1/c$: $a = 7.4063(3)$ Å, $b = 10.3739(5)$ Å, $c = 16.7642(8)$ Å, $\beta = 91.816(1)°$, $Z = 4$] and its 5-*N*-oxide **7(N5)** [$C_{18}H_{18}N_3OS$, triclinic, $P\bar{1}$: $a = 8.1510(7)$ Å, $b = 8.6106(7)$ Å, $c = 12.102(1)$ Å, $\alpha = 86.262(1)°$, $\beta = 83.364(1)°$, $\gamma = 74.711(1)°$, $Z = 4$] were structurally characterized and showed a significant helical distortion of the heterocyclic ring. Oxidation of **1** with NCS or triamine **12** with $PhI(OAc)_2$ led to a new heterocyclic ring system, ylide **13**. Both benzo[*c*]cinnoline **1** and ylide **13** were characterized spectroscopically and the absorption spectra were correlated with the results of ZINDO calculations.

Introduction

Despite a relatively large number of known benzo[*c*]cinnoline derivatives, there are very few with functionalized 1,10 positions.[1,2] Such compounds are potential precursors to new four-ring heterocycles (in addition to tetraazapyrene[3,4]) and derivatives with biological activity.[5]

In the context of developing a synthetic methodology for a new class of persistent radicals,[6] we focused on 1-amino-10-propylthiobenzo[*c*]cinnoline (**1**) as the key intermediate, which itself represents a class of unknown 1,10-heterodisubstituted benzo[*c*]cinnolines.

One of the most convenient ways to form benzo[*c*]cinnolines is the reduction of 2,2′-dinitrobiphenyls.[1,2] The reaction is general, effected by most typical reducing reagents,[1,2] and even sterically crowded 1,10-dialkyl[7−9] and naphtho[10] derivatives are obtained in good to excellent yields. The high propensity for the formation of benzo[*c*]cinnolines from nitrobiphenyls indicates that this might be the method of choice for preparation of **1**. Although rather rare, unsymmetrically substituted benzo[*c*]cinnolines are efficiently prepared via reductions of 2,2′-dinitrobiphenyls bearing aryl,[11,12] amino,[13] or additional nitro[5,14,15] groups. Therefore, the conversion of 2-propylthio-2′,6,6′-trinitrobiphenyl (**2**) to **1** was expected to be straightforward.



1 **2**

Here, we report the preparation of **1**, the first 1,10-heterodisubstituted benzo[*c*]cinnoline, from several precursors. The unusual course of reactions is rationalized with a mechanistic analysis. We also report the first molecular structure of a benzo[*c*]cinnoline *N*-oxide and demonstrate cyclization of **1** to a new tetracyclic heteroarene.

Results

Synthesis of 2-Propylthio-2′,6,6′-trinitrobiphenyl 2. The starting biphenyl **2** was prepared using the

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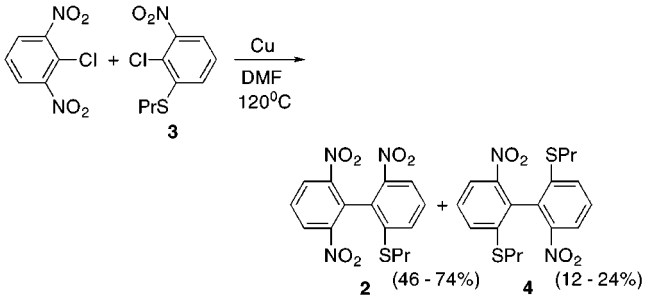
Scheme 1



Ullmann coupling reaction of 2,6-dinitrochlorobenzene and 2-chloro-3-nitropropylthiobenzene[16] (**3**) in DMF in the presence of activated copper powder (Scheme 1). The reaction gave the cross-coupling product **2** in up to 74% isolated yield. In addition, the homocoupling product **4** (12−24%) and small amounts of 1,3-dinitrobenzene and 2,2′,6,6′-tetranitrobiphenyl were also isolated.

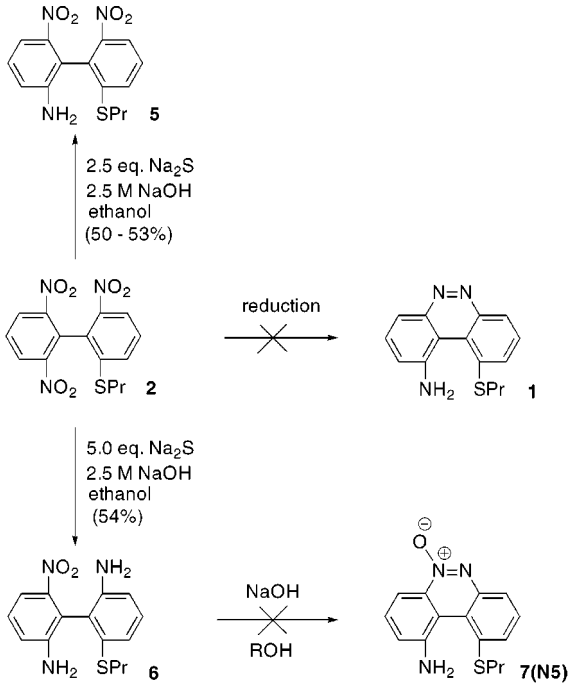
Benzo[*c*]cinnoline Ring-Closure Reactions. Initial attempts at formation of benzo[*c*]cinnoline **1** by reduction of trinitrobiphenyl **2** using standard literature methods were unsuccessful. Only when $LiAlH_4$[9,17] or $NaBH_4$/Pd−C[18] was used as the reducing reagent were small quantities of the benzo[*c*]cinnoline **1** detected by GC−MS in a complex mixture of products including those lacking the PrS group. Use of other reagents, such as $Na_2S{\cdot}9H_2O$,[19] Na_2S_x,[13] H_2/PtO_2,[19] or $N_2H_4{\cdot}H_2O$,[5] yielded mixtures containing products of partial or complete reduction of the starting material **2**, but no benzo[*c*]cinnoline **1** was detected. Full reduction also was achieved upon hydrogenation of **2** with Raney nickel under neutral or basic conditions.[4]

Although ineffective for the direct formation of benzo[*c*]cinnoline **1**, the sulfide reduction[19] using 2.5 equiv of $Na_2S{\cdot}9H_2O$ per nitro group proved useful for the practical preparation of the monoamino and diamino derivatives **5** and **6**, respectively (Scheme 2). Amine **5** was also prepared in about 80% yield using excess hydrazine hydrate[5] in the presence of Pd/C and Na_2CO_3 in refluxing ethanol.

Diamine **6** was envisioned as a precursor to the benzo[*c*]cinnoline *N*-oxide **7(N5)** in analogy to a literature precedence for similar systems.[20,21] Unfortunately, neither **7** nor **1** was observed and only starting material was recovered when **6** was treated with a base in either methanol[20] or 2-propanol[21] (Scheme 2).

The apparent sequential reduction of the nitro groups in trinitrobiphenyl **2** to the corresponding amines **5** and **6** shows that the amino group in **5** does not participate in the formation of the azo bridge of **1** and may even interfere with the reductive cyclization of the remaining two nitro groups. Therefore efforts were concentrated on N-protected aminodinitrobiphenyls **8** especially on the N-trifluoroacetyl derivative **8a**, whose deprotection occurs under mildly basic conditions.[22]

Scheme 2



Reduction of N-trifluoroacetyl derivative **8a** with the $Zn/CaCl_2$ system in ethanol, conditions which tolerate the protecting group, produced benzo[*c*]cinnoline-*N*-oxides in good yield (84% on a 0.50 mmol scale). The reaction and the yield, however, turned out to be scale-dependent and irreproducible. Larger scale preparations required longer reaction times and yields were usually poorer, e.g., 63% of the oxides on a 1.00 mmol scale. Surprisingly, however, GC−MS analysis showed that the starting amide **8a** undergoes initial full reduction to the protected triamino derivative **9a** *before* the benzo[*c*]cinnoline skeleton begins to form. These observations prompted more detailed mechanistic investigations.

Mechanistic Studies. The GC−MS results strongly suggested that the formation of the benzo[*c*]cinnoline skeleton is an oxidative process rather than reductive. If this were true, zinc metal would serve as the initial reducing reagent and atmospheric oxygen would be the oxidant. Support for this hypothesis was provided by a reaction of the amide **8a** with $Zn/CaCl_2$ in complete absence of air. Under these conditions, triamine **9a** was the sole product isolated in 79% yield even after a prolonged reaction time at ambient or elevated temperatures. Only upon contact of the reaction mixture with air did the benzo[*c*]cinnoline skeleton begin to form. In comparison, 2,2′-dinitrobiphenyl gave, according to GC−MS analysis, 92% of benzo[*c*]cinnoline and 8% of 2,2′-diaminobiphenyl when subjected to the same anaerobic reaction conditions.

The product of aerial oxidation appeared to be a 2:3 mixture of isomeric benzo[*c*]cinnoline *N*-oxides **10a**, which could be reduced with excess zinc to amide **11a** (Scheme 3). Without excess of zinc, the benzo[*c*]cinnoline *N*-oxides were isolated in 84% yield and, after deprotection, one of them, **7(N5)**, was separated and structurally characterized (vide infra).

Full deoxygenation of the oxides **10a** required additional amounts of zinc. In one experiment, benzo[*c*]cinnoline **1** was obtained in 69% yield based on trinitrobiphenyl **2** after deprotection of **11a** under the standard

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Scheme 3

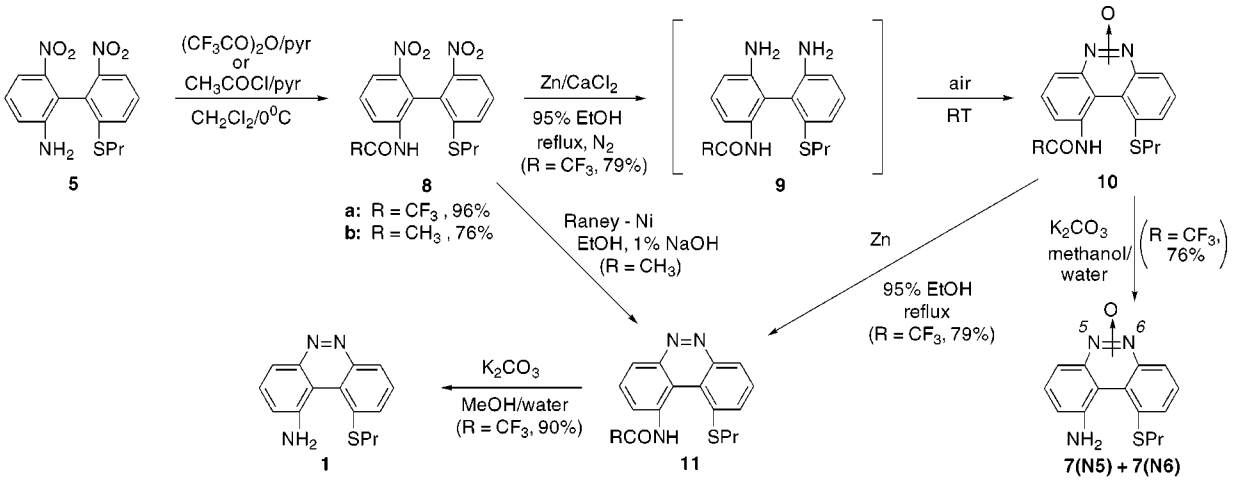
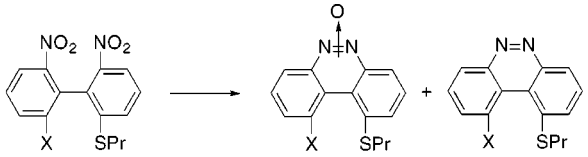


Table 1. Formation of Benzo[*c*]cinnoline Derivatives from Substituted Dinitrobiphenyls



compd	method[a]	benzo[*c*]cinnoline *N*-oxides yield, % (GC, %)	benzo[*c*]cinnoline yield, % (GC, %)	others yield, % (GC, %)
2, X = NO_2[b]	A	**7**, traces	**1**, traces	**5**, (54); **6**, (38)[c]
	B	not detected	not detected	
5, X = NH_2	A	**7**, 60 (80)	**1**, traces	**12**, (8)
	B	**7**, traces	**1**, 18 (22)	*c*
8a, X = $NHCOCF_3$	A	**10a**, 84 (90)	**11a**, (10), 79[d]	not detected
	B	**10a**, 66 (80)	**11a**, traces	**9a**, (9); **14a**, (11)[e]

[a] Method A: Zn/Cl_2 in EtOH; stirring at reflux in air for 12 h. Method B: Zn/Cl_2 in EtOH; stirring at reflux and under nitrogen for 2 h, then cooling to ambient temperature and passing air at about 1 bubble/sec for 12 h. [b] The nitro group is reduced to amino group in the product under the reaction conditions. [c] Unidentified, insoluble materials. [d] After further reduction of the benzo[*c*]cinnoline-*N*-oxides with 1 equiv of Zn. [e] $M^+ = 399$, matching structure **14a** or 2-amino-2′-nitro-6-propylthio-6′-trifluoroacetamidobiphenyl.

conditions, K_2CO_3 in methanol/water[22] (Scheme 3). The intermediates **10** and **11** were partially characterized and full characterization is provided for the free amines.

The formation of benzo[*c*]cinnoline *N*-oxide **10a** in the oxidative process turned out to be sensitive to the reaction conditions. When air was slowly passed through a mixture containing protected triamine **9a** prepared under anaerobic conditions, yield of benzo[*c*]cinnoline *N*-oxides **10a** was lower and relatively large amounts of intractable materials were produced. Benzo[*c*]cinnoline and the corresponding *N*-oxides were not detected in a sample of neat **9a** left in contact with air for 2 weeks, nor were they observed after 3 h of reflux followed by 12 h at ambient temperature in aerated ethanol containing $Zn(OH)_2/CaCl_2$. In the latter case, the starting amine **9a** was recovered in 91% yield. The best yields of the *N*-oxides **10a** were obtained when air was allowed to react at natural diffusion rate with the reaction mixture containing **8a** and the $Zn/CaCl_2$ system. Compound **8b** was converted to the corresponding *N*-oxides **10b** in the same manner. The outcome was analyzed via GC−MS, but without actual isolation of the products.

This rather unusual sequence of reactions, reduction−oxidation−cyclization−reduction, to form benzo[*c*]cinnoline **1** from the amide **8a**, raised some further questions and prompted studies of reduction of other substrates under similar reaction conditions. The results are collected in Table 1.

As is evident from Table 1, the results are highly dependent on the reaction conditions and nature of the substrate. Surprisingly, reduction of amine **5** under aerobic reaction conditions (method A) gave benzo[*c*]-cinnoline *N*-oxides **7** as the major product, while only traces of cyclic products were observed in the reduction of trinitrobiphenyl **2**. This demonstrates once again the unusual resistance of **2** to reductive cyclization.

The positive results from the reactions conducted in the presence of $Zn/CaCl_2$ prompted investigations of the reductions of **5** and **8** using methods that failed for preparation of **1** from **2**, especially the Raney nickel reduction.[4] The outcome of these reactions was largely dependent on the reaction conditions. Under neutral conditions, the hydrogenation led to the full reduction of the starting material, but in the presence of 1% NaOH benzo[*c*]cinnolines were formed in significant amounts. Thus, reduction of amine **5** under basic conditions gave 33% of the corresponding benzo[*c*]cinnoline **1** in addition to the triamine **12**, while the amide **8b** yielded a mixture of benzo[*c*]cinnoline *N*-oxides **10b** and benzo[*c*]cinnoline **11b** in approximate 4:1 ratio. The latter was identified by comparison to **11b**, prepared independently from **1** and acetyl chloride.

Preparation of 4-Propylcinnolino[5,4,3][*c,d,e*][1,2]-benzothiazine (13). The formation of the benzo[*c*]-cinnoline skeleton upon oxidation of triamines suggested the use of oxidants other than air. Most of the oxidants

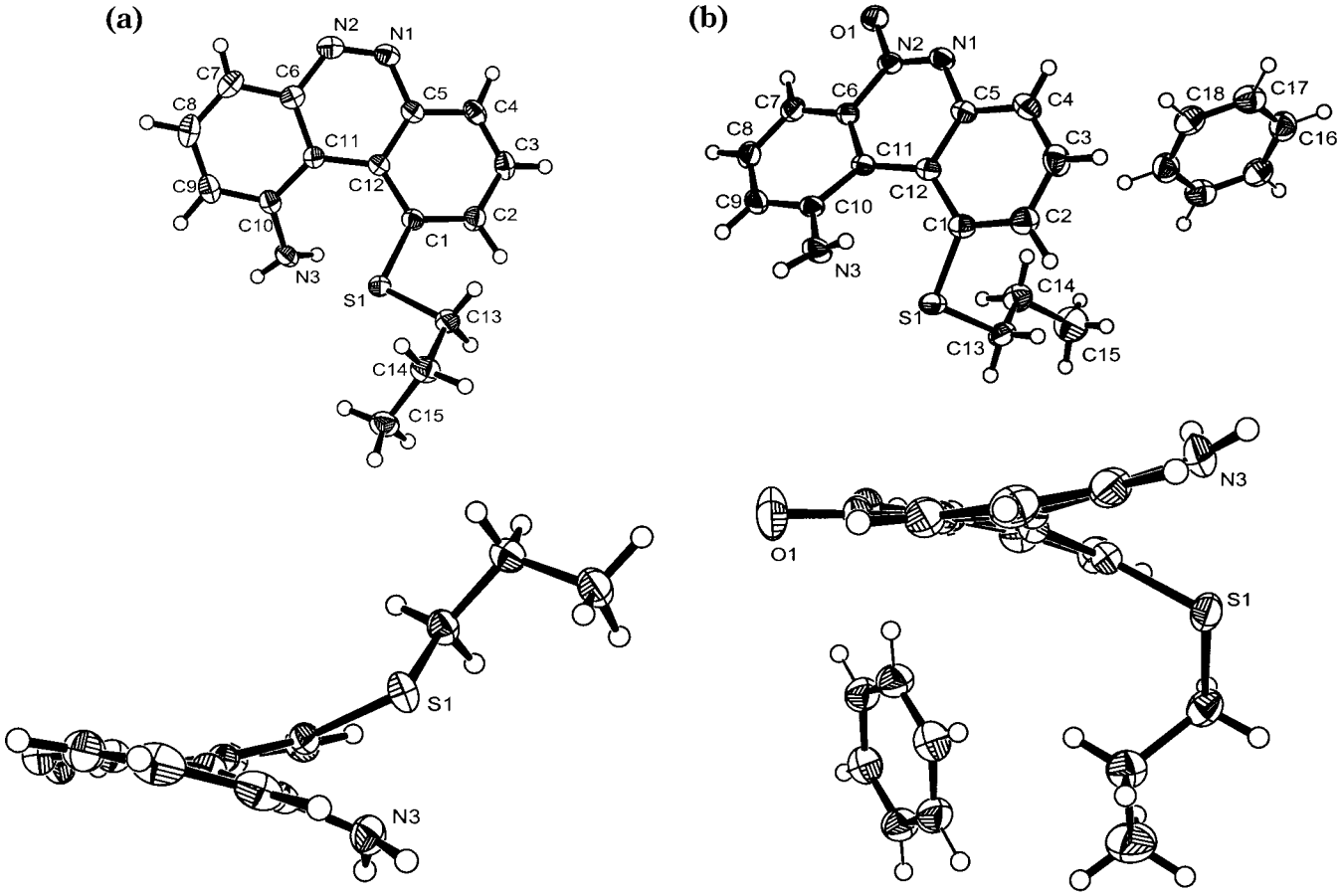


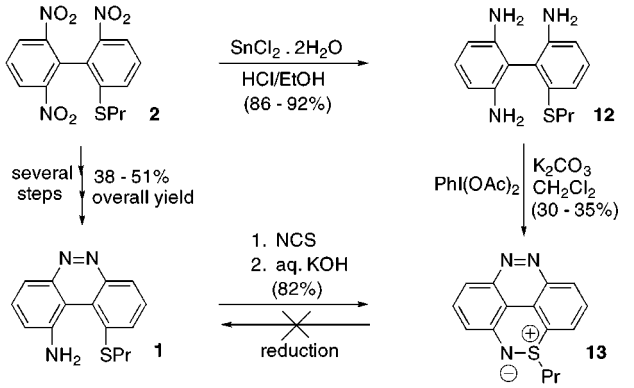
Figure 1. Two orientations of the X-ray structure of (a) 1-amino-10-propylthiobenzo[*c*]cinnoline (**1**) and (b) 1-amino-10-propylthiobenzo[*c*]cinnoline 5*N*-oxide (**7(N5)**). The thermal ellipsoids are drawn at 50% probability. Hydrogen atoms are given arbitrary radii.

generally employed in the formation of benzo[*c*]cinnolines,[1,2] are incompatible with the oxidant-sensitive sulfide functionality in the starting material. While the formation of sulfoxides and sulfones is undesired, formation of a sulfenamido N−S link upon oxidative cyclization is acceptable and even desired in the context of the project.[6] The latter may be accomplished with oxidants such as iodosobenzene derivatives, which have been used in similar cyclization reactions.[4,23] Thus, oxidation of the triamine **12** with iodobenzene diacetate in the presence of solid K_2CO_3 resulted in a closure of the cinnoline bridge and a concomitant formation of an N−S bond in ylide **13** (Scheme 4). The preparation of **13** proceeds with a reproducible yield of 30−35% based on the trinitrobiphenyl **2**. In the absence of base only traces of the ylide were detected by TLC.

The ylide **13** also was prepared in 82% yield from aminobenzo[*c*]cinnoline **1** (or 31−42% from **2**) by oxidative cyclization with NCS according to a general procedure.[24] Attempts at preparation of **1** by reduction of the N−S bond in **13** with $NaBH_4$, DIBAL-H, and $LiAlH_4$ were unsuccessful, and the starting material was fully recovered.

The ylide **13** exhibits a characteristic ^{1}H NMR pattern for the diastereotopic hydrogen atoms of the methylene group adjacent to the chiral sulfur center. In CD_2Cl_2 the signals appear at 2.51 and 3.01 ppm, respectively, and exhibit a doublet of doublets of doublets splitting pattern.

Scheme 4



Molecular and Crystal Structures for 1 and 7(N5). The benzo[*c*]cinnoline **1** forms monoclinic crystals ($P2_1/c$) while its oxide **7(N5)** cocrystallizes with benzene in the $P\bar{1}$ space group.[25] The molecular structures for both compounds are shown in Figure 1, and selected bond lengths and angles are listed in Table 2.

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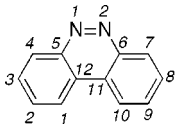
(25) Crystal data for **1**: $C_{15}H_{15}N_3S$ monoclinic, $P2_1/c$, a = 7.4063(3) Å, b = 10.3739(5) Å, c = 16.7642(8) Å, β = 91.816(1)°, V = 1287.4(1) Å^3, Z = 4, T = 173(2) K, λ = 0.71073 Å, $R(F^2)$ = 0.0359 (for 2528 reflections with $I > 2\sigma(I)$), $R(F^2)$ = 0.0425 (for all data, 2938 reflections). Crystal data for **7(N5)**: $C_{18}H_{18}N_3OS$ triclinic, $P\bar{1}$, a = 8.1510(7) Å, b = 18.6106(7) Å, c = 12.102(1) Å, α = 86.262(1)° β = 83.364(1)° γ = 74.711-(1)°, V = 813.3(1) Å^3, Z = 2, T = 173(2) K, λ = 0.71073 Å, $R(F^2)$ = 0.0368 (for 2938 reflections with $I > 2\sigma(I)$), $R(F^2)$ = 0.0484 (for all data, 3617 reflections). For details see the Supporting Information.

Table 2. Selected Experimental Bond Lengths (Å) and Angles (deg) for 1, 7(N5), Benzo[*c*]cinnoline (BC), 1,10-Dichlorobenzo[*c*]cinnoline-*N*,*N*′-dioxide (BCO-Cl_2) and 4,4′-Azoxyanisole (PAA)[a]



bond lengths and angles	1	7(N5)	BC[b]	BCO-Cl_2[c]	PAA[d]
N(1)−N(2)	1.287(2)	1.292(2)	1.292(3)	1.329	1.281(4)
N(1)−C(5)	1.393(2)	1.382(2)	1.401(4)	1.423	1.445(4)
N(2)−C(6)	1.394(2)	1.430(2)	1.392(3)	1.407	1.428(4)
C(11)−C(12)	1.447(2)	1.447(2)	1.436(3)	1.455	
N(2)−O(1)		1.275(2)		1.247, 1.262	1.288(3)
N(1)−N(2)−C(6)	120.16(13)	123.89(12)	119.9(2)	119.8	119.8(3)
N(2)−N(1)−C(5)	120.53(12)	118.19(11)	120.7(2)	120.2	116.5(3)
C(10)−C(11)−C(12)	127.08(13)	125.46(12)	124.9(2)	128.6	
C(1)−C(12)−C(11)	128.11(12)	127.28(12)	124.9(2)	128.3	
C(5)−N(1)−N(2)−C(6)	−9.4(2)	11.3(2)	0.3	−23.3	18.8(8)
C(1)−C(12)−C(11)−C(10)	26.5(2)	−29.6(2)	2.5	−30.6	

[a] Numbers in the scheme correspond to the crystallographic designation. [b] Data from ref 28. [c] Data from ref 26. Errors (or STD) are not available. [d] Data from ref 29.

The benzo[*c*]cinnoline skeleton in **1** and **7(N5)** is substantially distorted from planarity as a result of steric interactions of the amino and propylthio substituents in the 1 and 10 positions. The dihedral angles C(5)−N(1)−N(2)−C(6), characterizing the azo bridge, and C(1)−C(12)−C(11)−C(10) of the biphenyl junction are about 10° and 30°, respectively, and resemble those found in other sterically congested benzo[*c*]cinnolines[26] (Table 2). The torsional strain of the substituents also causes bending of both benzene rings by about 15° as measured for the angle between the C(1)−C(12)−C(5) and C(2)−C(3)−C(4) planes. On the basis of PM3 calculations for the parent benzo[*c*]cinnoline, the torsional strain in **1** is estimated to be about 5 kcal/mol.

The N(3) and S(1) atoms causing the helical geometry of the molecules are separated by about 2.84 Å in both compounds, which is 17% shorter than their van der Waals separation.[27]

Despite the significant torsional strain and the nonplanarity of the ring system, the interatomic distances in **1** are very similar to those found in the parent benzo[*c*]cinnoline[28] (Table 2). Introduction of an oxygen atom at the N(2) in **7(N5)** significantly affects only the N(2)−C(6) bond which is elongated by 0.03 Å and is similar to that found in 4,4′-azoxyanisole[29] (**PAA**).

The propyl chain in the oxide **7(N5)** adopts an all-trans conformation with gauche (65°) geometry at the S(1)−C(13) bond. In contrast, the propyl chain in **1** shows a gauche (60.3°) conformation at the C(13)−C(14) bond and close to trans (159.2°) arrangement at the S(1)−C(13) bond.

The crystal lattice of **7(N5)** consists of two antiparallel infinite chains of hydrogen-bonded benzo[*c*]cinnoline units alternating with a layer of aliphatic chains sandwiched off-center by two molecules of crystallization benzene. One of the two hydrogens of the amino group interacts with the azoxy bridge and the N(3)H···O(1) and N(3)H···N(1) distances are 2.198 and 2.550 Å, respectively.

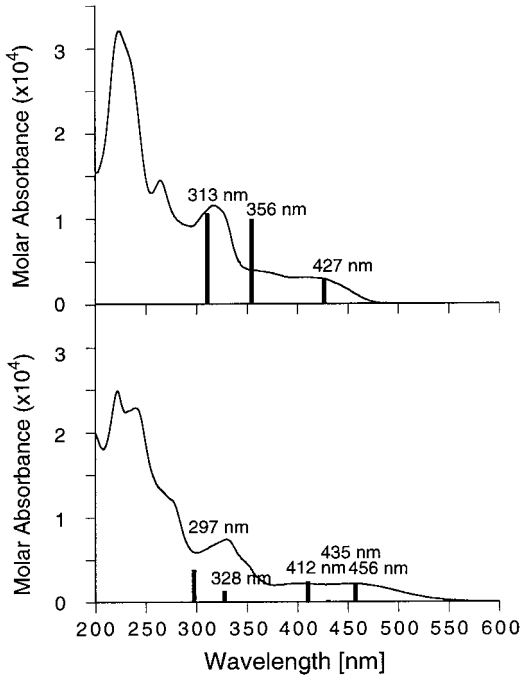


Figure 2. Electronic absorption spectrum for benzo[*c*]cinnoline **1** in cyclohexane and ylide **13** in acetonitrile. Vertical lines represent the ZINDO//PM3 calculated major transitions above 300 nm, scaled by 27×10^4 (**1**) and 2.0×10^4 (**13**).

Hydrogen bonding was also observed in the crystal structure of **1**. The protons of the amino group interact with N(3) of another amino group and N(1) of the azo bridge in the neighboring molecules. The N(3)H···N(1) and N(3)H···N(1) distances are 2.615 and 2.553 Å, respectively.

Electronic Absorption Spectra for 1 and 13. The UV−vis absorption spectra for the benzo[*c*]cinnoline **1** in cyclohexane and the ylide **13** in acetonitrile are shown in Figure 2. Attempts to measure the spectrum of **13** in cyclohexane were unsuccessful, due to low solubility and apparent instability of the ylide. The low energy portion of the spectrum of **1** consists of two low intensity bands at 427 and 373 nm (after deconvolution) and a more intense band at 318 nm. The absorption bands closely resemble those of the parent benzo[*c*]cinnoline,[30] red-

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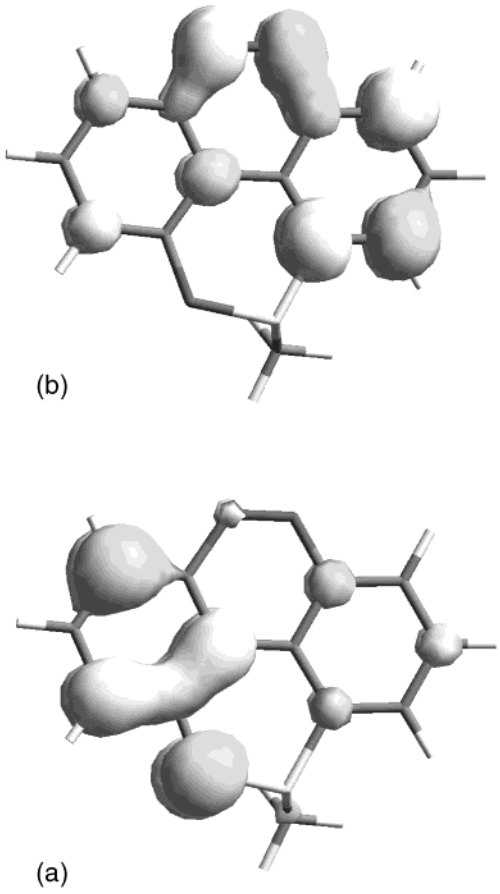


Figure 3. Representation of the HOMO (a) and the LUMO (b) calculated (ZINDO//PM3) for ylide **13**.

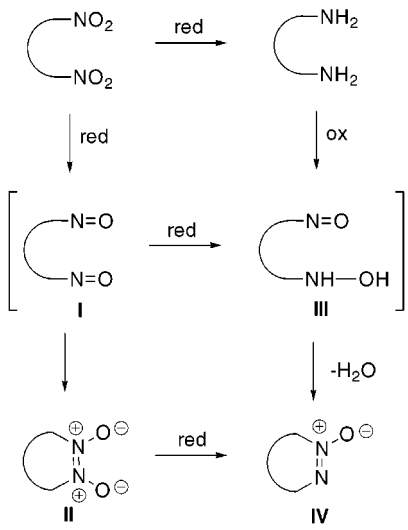
shifted by the presence of two auxochromes, NH_2 and SR, and the geometrical distortion of the chromophore. The bands can be assigned[31] as n−π* and π−π* (L_b and L_a), respectively, based on ZINDO//PM3 calculations for **1** and the parent benzo[*c*]cinnoline. The n−π* band of the parent heterocycle appears to be red shifted by 10 nm in **1**. According to the calculation, the n−π* transition is virtually unaffected by the substitution and ring bending while the π−π* L_b band is predicted to be red shifted by 33 nm.

The absorption spectrum of the ylide **13** is similar to that of benzo[*c*]cinnoline **1**, and it exhibits three bands at 453, 402, and 330 nm in the region above 300 nm. ZINDO//PM3 calculations show that the n−π* and π−π* transitions in the benzo[*c*]cinnoline skeleton are located at 435 and 328 nm, respectively, as shown in Figure 2. The long wavelength bands at 453 and 402 nm correspond well to the calculated absorption bands at 456 and 412 nm, which result from HOMO−LUMO and HOMO−LUMO + 1 transitions involving the N−S ylide electron manifold. The FMO's for the ylide are shown in Figure 3.

Discussion

Experimental results and mechanistic studies show that there are two main intramolecular processes leading to the formation of the benzo[*c*]cinnoline N=N bond in a biphenyl substrate:[1,2] dimerization of two nitroso groups (in **I**) to form *N*,*N*′-dioxide **II**[18,21,27,32] and base-promoted condensation of nitroso and hydroxylamino groups (in **III**) leading to the *N*-oxide **IV** (Scheme 5). Therefore, the feasibility of azo bridge formation will depend on the synchronous formation of the two nitrogen functionalities on the biphenyl and their favorable condensation reaction rates relative to other transformations of these transient species formed either during the reduction of NO_2 or the oxidation of NH_2 groups. This, in turn, is largely controlled by the steric and electronic effects of the substituents and also by reagents and reaction conditions.

Scheme 5



In some biphenyl substrates, the phenyl rings are electronicaly imbalanced, which affects the formation of intermediates **I** and **III**, while other substrates, having substituents at the 6- and 6′-positions, experience steric congestion, which decreases the rate of N−N bond formation. The trinitrobiphenyl **2**, amine **5** and amide **8** are the first examples of substrates in which both the electronic imbalance and steric congestion, evident from our X-ray studies, are simultaneously present in the same system. Both of these factors certainly contribute to the general failure of most standard methods in the formation of 1,10-disubstituted benzo[*c*]cinnoline **1** and several others.[2] Only two methods were found in the present studies to effect the cyclization: the $Zn/CaCl_2$ reduction−oxidation and Raney nickel reduction under basic conditions. Both work well for **5** and **8** but, curiously, not for trinitrobiphenyl **2**.

The observation of benzo[*c*]cinnoline *N*-oxides **7** and **10** as the major products in both reactions suggests that they are the primary cyclization products resulting from the condensation of nitrosohydroxylamine intermediates **III**, such as **14**. Further support for this hypothesis is provided by the GC−MS analysis of the reaction mixture, which shows transient species whose molecular ions match structure **14**. Raney nickel reduction conditions allow for the partial reduction of **8b** and effective trapping of the nitrosohydroxylamine intermediate (e.g., **14**), leading to the formation of **10b** and subsequent deoxygenation products.

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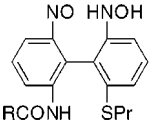

14

In contrast, the starting dinitrobiphenyls undergo full reduction with $Zn/CaCl_2$ to the corresponding amines, indicating that a nitrosohydroxylamine, for example **14**, is either not formed during the reduction or is too short-lived under the reaction conditions to form the N−N bond. The intermediate appears to be formed efficiently upon contact with air.

The mechanism of the oxidation of either the transient amine **12** or amide **9** is unclear. It is certain, however, that the reaction requires the initial presence of zinc metal and it does not work with zinc salts. This suggests that the key step might be a SET from Zn to O_2 to form the highly reactive superoxide anion $O_2^{\bullet-}$. Alternatively, transition metal impurities present in metallic zinc may catalyze the air oxidation of the amine.[33]

The literature data on similar processes is scarce. Several studies indicate that azobenzenes are among the products of autoxidation of anilines[34,35] but the formation of azoxybenzenes typically requires either a peroxide and more rigorous reaction conditions or a metal catalyst.[34] In either case, azobenzenes are always observed among the products. The observation of benzo[*c*]cinnoline *N*-oxide as the major product in the present case suggests a different mechanism of oxidation.

The formation of the tetracyclic ylide **13** is also noteworthy. The tendency for the formation of the skeleton of **13** and the resistance of the N−S bond to cleavage can be inferred from the helical structure of **1**. Thus, the NCS oxidation of **1** closes the N−S bond in **13**, alleviating the torsional strain in the substrate. The double cyclization of triamine **12** with $PhI(OAc)_2$[36] gave **13** in about twice higher yield than that for the analogous preparation of the 4,5,9,10-tetraazapyrene ring.[4] This remarkable result can be attributed to the presence of a base[37] in the reaction mixture, which presumably favors an ionic mechanism.

Conclusions

The compounds reported here (**1**, **7**, **10**, and **11**) are the first examples of 1,10-heterodisubstituted benzo[*c*]-cinnolines and benzo[*c*]cinnoline *N*-oxides. Their preparation was accomplished only under two specific reaction conditions: reduction with basic Raney nickel and reduction with $Zn/CaCl_2$−air both yielding the corresponding *N*-oxides as primary cyclization products. Detailed studies of the latter reaction prompted the proposal of a complex reduction−oxidation−cyclization mechanism which requires atmospheric oxygen. The individual steps are not entirely clear at present and merit further investigation since such a mechanism may operate in some other cases, especially with electronically unbalanced or strained systems but not with 2,2′-dinitrobiphenyl.

The efficiency of the overall redox process with zinc and atmospheric oxygen has proven difficult to control due to the heterogeneous nature of the three-phase reaction system. The amount of oxygen needed for the reaction is also critical and needs to be carefully controlled, since its excess causes the formation of resinous materials. On the other hand, the reproducible Raney nickel reductive cyclization requires a base which is less tolerant of some functional and protective groups.

The main difficulty with formation of 1,10-heterodisubstituted benzo[*c*]cinnoline **1** has been attributed to a build-up of steric strain resulting from close contact of the two substituents. This steric interaction causes a significant geometrical distortion of the heterocyclic ring, which has been estimated at about 5 kcal/mol.

The formation of an N−S bond alleviates the torsional strain in **1** and leads to a new heterocyclic ring system, ylide **13**. A one-pot double ring closure with hypervalent iodine reagents and the simultaneous formation of the azo and sulfiliminyl bridges in the tetracyclic ylide **13** proceeds with good yield and represents a useful extension of classical methods for formation of sulfilimines with NCS. This method also provides a much shorter route to **13** (two steps vs six, starting from compound **2**), combined with a better and reproducible overall yield of about 30%.

Synthetic methodology and mechanistic studies described here can, in principle, be extended to other bay-substituted benzo[*c*]cinnolines and tetracyclic heteroarenes.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in C_6D_6 at 300 and 75.4 MHz, respectively, and referenced to the solvent, unless specified otherwise. IR spectra were recorded by deposition of a thin film from solution onto sodium chloride disks. Liquid chromatography separations were carried out on Silica Gel 60 (230−400 mesh). Zn dust, used for the redox experiments, was purchased from the Aldrich chemical company (Catalog no. 20,998-8, 325 mesh size). Elemental analysis was provided by Atlantic Microlab, Norcross, GA.

Semiempirical PM3 calculations were carried out using the Gaussian 94 package[38] on SGI R8000 workstation. Electronic spectra were calculated using ZINDO (INDO/2, 30 × 30 CI) in the Cerius2 suite of programs using PM3-optimized geometries.

X-ray data collection and structure solution were conducted at the X-ray Crystallographic Laboratory, 160 Kolthoff Hall, Department of Chemistry, University of Minnesota. All calculations were performed using SGI INDY R4400-SC or Pentium computers using the SHELXTL V5.0 suite of programs.

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X-ray Crystallography for 1-Amino-10-propylthiobenzo[*c*]cinnoline (1). An orange crystal (approximate dimensions 0.35 × 0.23 × 0.21 mm) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Siemens SMART system for a data collection at 173(2)K. A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrixes determined from 68 reflections. Final cell constants were calculated from the xyz centroids of 6325 strong reflections from the actual data collection after integration (SAINT 6.01, 1999). After the final refinement a difference peak remains in the vicinity of N(2) at a distance of 1.05 Å. This electron density is believed to belong to an impurity (Compound **7(N5)**). An oxygen atom refines at this site with an occupancy of approximately 8%, which improves R_1 from 0.0359 to 0.0320. However, the distance of 1.05 Å is too short for an N−O bond. For this report the presence of the impurity was neglected.

X-ray Crystallography for 1-Amino-10-propylthiobenzo[*c*]cinnoline 5*N*-Oxide (7(N5)). An orange crystal (approximate dimensions 0.28 × 0.26 × 0.04 mm) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Siemens SMART system for a data collection at 173(2)K. A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrixes determined from 54 reflections. Final cell constants were calculated from the *xyz* centroids of 3700 strong reflections from the actual data collection after integration (SAINT 6.01, 1999).

1-Amino-10-propylthiobenzo[*c*]cinnoline (1). Benzo[*c*]-cinnoline **11** (0.15 g, 0.41 mmol) was dissolved in a mixture of MeOH (15 mL) and water (3 mL), and solid anhydrous K_2CO_3 (0.50 g, 3.62 mmol) was added. The mixture was stirred at reflux for 6 h and the progress of the reaction was monitored by TLC. Methanol was removed, and the residue was extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and the solvent removed. The crude material was separated on a silica gel column (benzene−EtOAc, 3:1 ratio) to give 0.10 g (90% yield) of reddish-brown material. Additional purification was performed by preparing a concentrated solution in benzene and very slowly evaporating the solvent. This resulted in large, reddish-brown, cubical crystals: mp 89−90 °C; ^{1}H NMR δ 0.43 (t, J = 7.3 Hz, 3H), 0.83−0.93 (m, 2H), 2.12 (t, J = 7.1 Hz, 2H), 4.43 (bs, 2H), 6.47 (dd, J_1 = 7.8 Hz, J_2 = 0.9 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.53 (dd, J_1 = 7.5 Hz, J_2 = 1.1 Hz, 1H), 8.29 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H); ^{13}C NMR δ 13.1, 22.11, 37.2, 107.9, 116.7, 119.3, 121.1, 127.3, 129.1, 129.9, 132.8, 134.2, 144.4, 146.5, 148.2; IR ν_{max} 3330 and 3216 (N−H), 1429 (N=N) cm^{-1}; UV (cyclohexane) λ_{max} (log ϵ) 410 (3.48), 318 (4.06), 265 (4.16) and 223 (4.50) nm; MS *m/e* 269 (M$^+$, 75), 223 (100). Anal. Calcd for $C_{15}H_{15}N_3S$: C, 66.89; H, 5.61; N, 15.59. Found: C, 66.68; H, 5.54; N, 15.55.

2,2′,6-Trinitro-6′-propylthiobiphenyl (2) and 2,2′-Bis-(propylthio)-6,6′-dinitrobiphenyl (4). A mixture of 2-chloro-3-nitropropylthiobenzene[16] (**3**, 2.05 g, 8.90 mmol), 2,6-dinitrochlorobenzene (2.16 g, 10.70 mmol), and activated copper (2.16 g, 33.20 mmol) in dry DMF (30 mL) was stirred for 20 h at 120 °C under a stream of nitrogen. The reaction mixture was poured into dilute HCl and the organic components were extracted with methylene chloride. The organic layer was washed several times with water, dried ($MgSO_4$) and passed through a Celite plug. The solvent was removed under reduced pressure and the residual mixture was separated on a silica gel column (hexanes−acetone, 6:1 ratio). The first fraction (0.07 g) was identified as 1,3-dinitrobenzene (0.07 g, 0.41 mmol, 5%), and the second as 2,2′-dinitro-6,6′-bispropylthiobiphenyl **4**, isolated as a dark-yellow solid (0.32 g, 18% yield), which upon recrystallization from ethanol yielded yellow crystals: mp 117−118 °C; ^{1}H NMR δ 0.58 (t, J = 7.4 Hz, 3H), 1.12−1.24 (m, 2H), 2.20 (t, J = 7.9 Hz, 2H), 6.75 (t, J = 7.9 Hz, 2H), 6.93 (d, J = 7.9 Hz, 2H), 7.70 (dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.3, 21.8, 34.9, 121.2, 129.1, 130.4, 131.2, 140.7, 148.1; MS *m/e* 392 (M$^+$, 100), 346 (97). Anal. Calcd for $C_{18}H_{20}N_2O_4S_2$: C, 55.10; H, 5.14; N, 7.14. Found: C, 55.19; H, 5.04; N, 7.15.

The last fraction was the trinitrobiphenyl **2**, isolated as a dark-yellow solid (2.39 g, 74% yield). Recrystallization from ethanol gave yellow needles: mp 118−119 °C; ^{1}H NMR δ 0.52 (t, J = 7.4 Hz, 3H), 1.03−1.11 (m, 2H), 2.07 (t, J = 7.4 Hz, 2H), 6.39 (t, J = 8.2 Hz, 1H), 6.66 (t, J = 8.2 Hz, 1H), 6.76 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.67 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.1, 35.7, 122.1, 127.4, 128.3, 129.7, 130.2, 130.4, 132.3, 140.0, 148.7, 149.1; IR ν_{max} 1526 and 1347 (NO_2) cm^{-1}; MS *m/e* 363 (M$^+$, 67), 229 (100). Anal. Calcd for $C_{15}H_{13}N_3O_6S$: C, 49.59; H, 3.61; N, 11.56. Found: C, 49.50; H, 3.58; N, 11.61.

2-Amino-2′,6-dinitro-6′-propylthiobiphenyl (5). $Na_2S\cdot 9H_2O$ (2.17 g, 9.00 mmol) in 2 M NaOH (5 mL) was added in one portion to a solution of trinitrobiphenyl **2** (1.34 g, 3.70 mmol) dissolved in abs. EtOH (60 mL) at 70 °C, and the resulting mixture was stirred at reflux for 2 h. Ethanol was removed and the solid residue was extracted with methylene chloride. The organic extract was dried (Na_2SO_4) and passed through a silica gel plug. The solvent was removed and the residue was separated on a silica gel column (methylene chloride) to give 0.65 g (53% yield) of the amine as a bright-yellow solid. The reaction takes place with a reproducible yield of 50−53%. In one instance the compound was obtained with 76% yield. Additionally purified via recrystallization from ethanol: mp 174−175 °C; ^{1}H NMR δ 0.58 (t, J = 7.4 Hz, 3H), 1.08−1.20 (m, 2H), 2.15 (t, J = 7.3 Hz, 2H), 2.80 (bs, 2H), 6.16 (d, J = 8.2 Hz, 1H), 6.67 (t, J = 8.0 Hz, 1H), 6.72 (t, J = 7.9 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 7.37 (dd, J_1 = 8.2 Hz, J_2 = 0.9 Hz, 1H), 7.46 (dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.5, 21.6, 33.4, 111.8, 112.4, 115.2, 120.4, 121.3, 127.7, 129.9, 131.3, 141.1, 148.2, 148.7, 149.5; IR ν_{max} 3469 and 3382 (N−H), 1523 and 1349 (NO_2) cm^{-1}; MS *m/e* 333 (M$^+$, 67), 287 (65), 245 (100). Anal. Calcd for $C_{15}H_{15}N_3O_4S$: C, 54.05; H, 4.54; N, 12.60. Found: C, 54.08; H, 4.53; N, 12.55.

2,2′-Diamino-6-nitro-6′-propylthiobiphenyl (6). Reduction of trinitrobiphenyl **2** (1.34 g, 3.70 mmol) with $Na_2S\cdot 9H_2O$ (4.34 g, 18.00 mmol) in 2 M NaOH (10 mL) was conducted as described for **5**. The crude material was separated on a silica gel column (hexane−EtOAc, 2:1 ratio) to give 0.60 g (54% yield) of the diamine as a dark orange solid. Additional purification was performed via recrystallization from methanol: mp 110−111 °C; ^{1}H NMR δ 0.68 (t, J = 7.3 Hz, 3H), 1.30−1.40 (m, 2H), 2.40−2.47 (m, 2H), 3.11 (bs, 2H), 3.36 (bs, 2H), 6.29 (dd, J_1 = 8.1 Hz, J_2 = 0.9 Hz, 1H), 6.34 (dd, J_1 = 8.1 Hz, J_2 = 1.1 Hz, 1H), 6.62 (dd, J_1 = 8.1 Hz, J_2 = 1.1 Hz, 1H), 6.77 (t, J = 8.1 Hz, 1H), 6.99 (t, J = 8.0 Hz, 1H), 7.20 (dd, J_1 = 8.1 Hz, J_2 = 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 34.8, 113.2, 114.1, 115.5, 117.3, 118.0, 119.2, 130.0, 130.1, 138.4, 145.6, 146.9, 151.3; IR ν_{max} 3464 and 3368 (N−H), 1517 and 1353 (NO_2) cm^{-1}; MS *m/e* 303 (M$^+$, 18), 215 (100). Anal. Calcd for $C_{15}H_{17}N_3O_2S$: C, 59.39; H, 5.65; N, 13.84. Found: C, 59.32; H, 5.70; N, 13.72.

1-Amino-10-propylthiobenzo[*c*]cinnoline *N*-Oxides (7). Amide **8a** (0.31 g, 0.72 mmol) was dissolved in 95% ethanol (20 mL) and Zn dust (0.21 g, 3.20 mmol) and $CaCl_2$ (0.14 g, 1.26 mmol) were added to the solution. The mixture was stirred at reflux for 1 h, then stirring was continued at ambient temperature for 12 h. Water and methylene chloride were added, and the organic layer was separated, dried ($MgSO_4$), and passed through a short silica gel pad. The solvent was removed to yield 0.23 g (84%) of crude mixture of 1-propylthio-10-trifluoroacetamidobenzo[*c*]cinnoline *N*-oxides (**10**). The material was dissolved in methanol (15 mL) and water (5 mL), and anhydrous K_2CO_3 (0.50 g) was added. The mixture was stirred at reflux for 6 h and cooled, and methanol was removed. Methylene chloride was added, the organic layer was separated and dried ($MgSO_4$), and the solvent was removed. The residue was separated on a silica gel column (hexane−EtOAc, 2:1 ratio), and two intensely colored fractions with similar mobility were collected. The more mobile yellow fraction yielded a reddish solid which was recrystallized from hexane−benzene

(4:1 ratio) to yield red needles of **7(N5)** (0.06 g, 30% yield based on **8a**): mp 136−137 °C; ^{1}H NMR δ 0.49 (t, J = 7.3 Hz, 3H), 0.94−1.01 (m, 2H), 2.14 (t, J = 7.2 Hz, 2H), 4.21 (bs, 2H), 6.29 (dd, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H), 6.99 (t, J = 7.7 Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H), 7.29 (dd, J_1 = 7.6 Hz, J_2 = 1.1 Hz, 1H), 7.64 (dd, J_1 = 8.0 Hz, J_2 = 1.1 Hz, 1H), 8.31 (dd, J_1 = 8.3 Hz, J_2 = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 13.3, 22.5, 37.6, 109.7, 115.0, 118.2, 118.6, 123.9, 128.7, 130.6, 132.1, 133.2, 140.2, 143.4, 145.2; IR ν_{max} 3334 and 3217 (N−H) cm^{-1}. Anal. Calcd for $C_{15}H_{15}N_3OS$ x 0.5 C_6H_6: C, 66.64; H, 5.59; N, 12.95. Found: C, 66.35; H, 5.53; N, 13.09.

The less mobile dark red fraction yielded a solid material, which upon recrystallization gave reddish-brown crystals (0.09 g, 46% yield based on **8a**). NMR analysis indicated it to be a mixture of **7(N5)** and **7(N6)** and the ^{1}H NMR spectrum of **7(N6)** was elucidated from the difference of the spectra for the mixture and that for the pure **7(N5)**: ^{1}H NMR δ 0.49 (t, J = 7.3 Hz, 3H), 0.90−1.01 (m, 2H), 2.13 (t, J = 7.1 Hz, 2H), 4.02 (bs, 2H), 6.27 (dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H), 6.87 (dd, J_1 = 8.3 Hz, J_2 = 7.7 Hz, 1H), 7.10 (t, J = 7.9 Hz, 1H), 7.33 (dd, J_1 = 7.6 Hz, J_2 = 1.3 Hz, 1H), 7.37 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 8.64 (dd, J_1 = 8.4 Hz, J_2 = 1.3 Hz, 1H). Anal. Calcd for $C_{15}H_{15}N_3OS$: C, 63.14; H, 5.30; N, 14.72. Found: C, 63.23; H, 5.31; N, 14.78.

2,2′-Dinitro-6-propylthio-6′-trifluoroacetamidobiphenyl (8a). Amine **5** (1.13 g, 3.40 mmol) was treated with trifluoroacetic anhydride (1.13 g, 5.10 mmol, 0.76 mL) in dry methylene chloride (10 mL) and pyridine (0.38 g, 5.10 mmol, 0.38 mL) at 0 °C. The reaction mixture was gradually warmed to ambient temperature, and stirring was continued for 3 h. The mixture was washed with water (×3). The organic layer was dried ($MgSO_4$), passed through a silica gel plug and the solvent removed to give 1.40 g (96% yield) of the amide as a pale yellow glass: ^{1}H NMR δ 0.51 (t, J = 7.1 Hz, 3H), 1.00−1.06 (m, 2H), 1.99−2.06 (m, 2H), 6.64 (t, J = 8.1 Hz, 1H), 6.68 (t, J = 8.7 Hz, 1H), 6.72 (dd, J_1 = 8.1 Hz, J_2 = 1.1 Hz, 1H), 7.26 (dd, J_1 = 1.1 Hz, J_2 = 8.1 Hz, 1H), 7.39 (dd, J_1 = 1.1 Hz, J_2 = 8.3 Hz, 1H), 7.51 (bs, 1H), 8.05 (dd, J_1 = 1.0 Hz, J_2 = 8.3 Hz, 1H); ^{13}C NMR δ 13.0, 21.5, 34.0, 114.1 and 117.9 (CF_3), 120.5, 122.5, 123.3, 124.7, 128.5, 129.9, 130.3, 130.4, 134.8, 141.6, 148.6, 150.2, 154.5 and 155.0 (CO); IR ν_{max} 3401 and 3322 (N−H), 1741 (C═O), 1530 and 1350 (NO_2) cm^{-1}; MS *m/e* 429 (M$^+$, 7), 295 (100). Anal. Calcd for $C_{19}H_{14}F_3N_2O_5S$: C, 47.55; H, 3.29; N, 9.78. Found: C, 48.05; H, 3.62; N, 9.48.

2-Acetamido-2′,6-dinitro-6′-propylthiobiphenyl (8b). Amine **5** (0.22 g, 0.66 mmol), dissolved in dry methylene chloride (5 mL), was treated with acetyl chloride (0.06 g, 0.79 mmol, 0.06 mL) and pyridine (0.06 g, 0.79 mmol, 0.06 mL) at 0 °C. The mixture was stirred for 3 h at ambient temperature and poured into water, and the organic layer was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude product (0.22 g) was dissolved upon heating in a mixture of hexane−EtOAc (5:1 ratio). The solution was rapidly cooled to −20 °C, and the separated solid was filtered off. Subsequent recrystallization from 50% ethanol gave 0.19 g (76% yield) of yellow crystals: mp 134−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3H), 1.55−1.64 (m, 2H), 1.94 (s, 3H), 2.84 (t, J = 7.2 Hz, 2H), 6.68 (bs, 1H), 7.58−7.60 (m, 2H), 7.63 (t, J = 8.2 Hz, 1H), 7.91 (dd, J_1 = 6.5 Hz, J_2 = 2.8 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 8.56 (bs, 1H); IR ν_{max} 3367 and 3297 (N−H), 1692 (C═O), 1527 and 1348 (NO_2) cm^{-1}; MS *m/e* 375 (M$^+$, 8), 245 (100). Anal. Calcd for $C_{17}H_{17}N_3O_5S$: C, 54.39; H, 4.56; N, 11.19. Found: C, 54.27; H, 4.55; N, 11.10.

2,2′-Diamino-6-propylthio-6′-trifluoroacetamidobiphenyl (9a). A mixture of amide **8a** (0.116 g, 0.27 mmol) and PtO_2 (0.012 g, 0.05 mmol) in 10 mL of EtOH−EtOAc mixture (4:1 ratio) was hydrogenated at 50 psi for 4 h at ambient temperature. The resulting colorless solution was filtered through a Celite pad and the solvent removed. The residue was separated on a silica gel column (hexane−EtOAc, 2:1 ratio) to give 0.08 g (82% yield) of the diamine as a pale yellow oil which solidified upon standing: mp 84−85 °C; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.97 (t, J = 7.3 Hz, 3H), 1.58−1.65 (m, 2H), 2.74−2.85 (m, 2H), 3.68 (bs, 4H), 6.65 (dd, J_1 = 8.0 Hz, J_2 = 0.9 Hz, 1H), 6.72 (dd, J_1 = 8.1 Hz, J_2 = 1.0 Hz, 1H), 6.76 (dd, J_1 = 7.9 Hz, J_2 = 0.7 Hz, 1H), 7.69 (bs, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.28 (t, J = 8.1 Hz, 1H), 7.61 (dd, J_1 = 8.1 Hz, J_2 = 0.7 Hz, 1H); IR ν_{max} 3378 (N−H), 1728 (C═O) cm^{-1}; HRMS (FAB$^+$) *m/z* calcd for $C_{17}H_{19}F_3N_3OS$ [M + H]$^+$ 370.1201, found 370.1190.

Formation of Benzo[*c*]cinnoline Derivatives. Method A. In a typical run, 1 equiv of starting biphenyl was mixed with 1.9 equiv of Zn dust and 0.75 equiv of $CaCl_2$ per nitro group in 96% EtOH. The mixture was stirred and refluxed for 12 h, poured into water, and extracted with ether. The organic extract was dried ($MgSO_4$) and filtered through a short silica gel pad. The solvent was removed under reduced pressure, and the residue was further separated on a silica gel column. Results are shown in Table 1.

Method B. In a typical run, 1 equiv of starting biphenyl was mixed with 1.9 equiv of Zn dust and 0.75 equiv of $CaCl_2$ per nitro group in 96% EtOH. The mixture was carefully degassed through three cycles of the freeze−pump−thaw procedure. It was then placed under positive nitrogen pressure and refluxed for 2 h. The heating was discontinued, and air was passed through the stirred mixture for 12 h at the rate of about 1 bubble/s. The mixture was poured into water and extracted with ether. The organic extract was dried ($MgSO_4$) and filtered through a short silica gel pad. The solvent was removed under reduced pressure and the residue was further separated on a silica gel column. Results are shown in Table 1.

1-Propylthio-10-trifluoroacetamidobenzo[*c*]cinnoline *N*-Oxides (10a). From **8a** (0.31 g, 0.73 mmol), according to method A. The crude mixture was separated on a silica gel column (hexane−EtOAc, 2:1 ratio) to give 0.23 g (84% yield) of a yellow glass. ^{1}H NMR analysis indicated it to be a mixture of both *N*-oxides in a 2:1 ratio, and the individual spectra were elucidated on the basis of integral intensity differences: ^{1}H NMR (major component) δ 0.57 (t, J = 7.3 Hz, 3H), 1.00−1.12 (m, 2H), 2.32 (t, J = 7.2 Hz, 2H), 6.89−6.91 (m, 2H), 7.10−7.21 (signals for 2H, not resolved), 8.12 (dd, J_1 = 8.0 Hz, J_2 = 1.1 Hz, 1H), 8.20 (dd, J_1 = 8.5 Hz, J_2 = 1.2 Hz, 1H), 9.64 (bs, 1H); ^{1}H NMR (minor component) δ 0.55 (t, J = 7.3 Hz, 3H), 1.00−1.12 (m, 2H), 2.25 (t, J = 7.3 Hz, 2H), 6.85 (t, J = 8.4 Hz, 1H), 7.10−7.21 (signals for 2H, not resolved), 7.29 (dd, J_1 = 7.7 Hz, J_2 = 1.0 Hz, 1H), 7.74 (dd, J_1 = 8.4 Hz, J_2 = 1.1 Hz, 1H), 8.04 (dd, J_1 = 7.5 Hz, J_2 = 1.7 Hz, 1H), 9.76 (bs, 1H); MS (major peak with retention time 16.50 min or minor peak at 16.70 min) *m/e* 381 (M$^+$, 33), 365 (11), 306 (100).

1-Propylthio-10-trifluoroacetamidobenzo[*c*]cinnoline (11a). A mixture of benzo[*c*]cinnoline *N*-oxides **10** (0.22 g, 0.52 mmol) was dissolved in 95% ethanol (15 mL), and Zn dust (0.15 g, 2.40 mmol) and $CaCl_2$ (0.10 g, 0.75 mmol) were added to the solution. The mixture was stirred at reflux for 1 h, cooled to ambient temperature, and then stirred for 12 h. Zn dust (0.10 g, 1.60 mmol) was added, and the mixture was refluxed for 1.5 h. The solvent was removed under reduced pressure. Water and methylene chloride were added to the residue, and the organic layer was separated, dried ($MgSO_4$), and passed through a silica gel pad. The solvent was removed and the residue separated on a silica gel column (benzene−EtOAc, 8:1 ratio) to yield 0.15 g (79% yield) of intensely yellow material. It was sufficiently pure to be used for further preparations: ^{1}H NMR δ 0.42 (t, J = 7.3 Hz, 3H), 0.80−0.91 (m, 2H), 2.06 (t, J = 7.1 Hz, 2H), 7.07 (t, J = 7.8 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.37 (dd, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H), 8.09 (d, J = 7.9 Hz, 1H), 8.24 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H), 8.38 (dd, J_1 = 7.9 Hz, J_2 = 1.0 Hz, 1H), 9.11 (bs, 1H); MS *m/e* 365 (M$^+$, 47), 290 (100).

1-Acetamido-10-propylthiobenzo[*c*]cinnoline (11b). Compound **1** (0.03 g, 0.09 mmol) and triethylamine (0.01 g, 0.09 mmol, 0.01 mL) were dissolved in dry methylene chloride (2 mL). Acetyl chloride (0.01 g, 0.09 mmol, 0.01 mL) in dry methylene chloride (1 mL) was added dropwise at 0−5 °C and stirring was continued for 2 h at ambient temperature. The mixture was washed with water, the organic layer was dried ($MgSO_4$) and the solvent removed. The residue was separated on a silica gel column (hexane−EtOAc, 1:1 ratio) to give 0.025 g (79% yield) of yellow solid. Additional purification via

subsequent recrystallization from 50% EtOH: mp 156−157 °C; ^{1}H NMR (acetone-d_6) δ 0.72 (t, J = 7.3 Hz, 3H), 1.17−1.30 (m, 2H), 2.16 (s, 3H), 2.79 (t, J = 7.3 Hz, 2H), 7.86 (t, J = 7.8 Hz, 1H), 7.96 (t, J = 7.9 Hz, 1H), 8.03 (d, J = 7.2 Hz, 1H), 8.32 (d, J = 7.7 Hz, 1H), 8.41 (d, J = 8.0 Hz, 2H), 9.28 (bs, 1H); ^{13}C NMR (acetone-d_6) δ 13.3, 22.9, 24.1, 39.6, 114.3, 121.7, 126.3, 127.2, 128.3, 129.5, 130.0, 133.7, 135.9, 136.8, 146.7, 147.2, 168.4; IR ν_{max} 3256 (N−H), 1669 (C═O), 1430 (N═N) cm^{-1}; MS *m/e* 311 (M$^+$, 7), 236 (100). Anal. Calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.28; H, 5.44; N, 13.43.

2,2′,6-Triamino-6′-propylthiobiphenyl (12). Trinitrobiphenyl **2** (0.31 g, 0.85 mmol) was dissolved in EtOH (4 mL) and HCl (4 mL) upon heating. $SnCl_2 \cdot 2H_2O$ (1.77 g, 7.84 mmol) was added, and the mixture was stirred at 100 °C for 0.5 h. Aqueous NaOH was added in excess and organic material was extracted with ether. The organic layer was dried (Na_2SO_4) and the solvent removed. The crude product was purified on a silica gel column (hexane−EtOAc, 1:1 ratio) to give 0.21 g (90% yield) of a pale yellow oil: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.99 (t, J = 7.4 Hz, 3H), 1.59−1.66 (m, 2H), 2.79 (t, J = 7.3 Hz, 2H), 3.49 (bs, 6H), 6.21 (d, J = 8.0 Hz, 2H), 6.60 (dd, J_1 = 8.0 Hz, J_2 = 0.9 Hz, 1H), 6.71 (dd, J_1 = 7.9 Hz, J_2 = 0.8 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 14.2, 23.0, 34.2, 106.1, 107.9, 112.6, 115.8, 117.8, 130.2, 130.6, 140.6, 146.4, 146.6; IR ν_{max} 3442 and 3348 (N−H) cm^{-1}; MS *m/e* 273 (M+, 65), 214 (29), 198 (100); HRMS (FAB$^+$) *m/z* calcd for $C_{15}H_{20}N_3S$ [M + H]$^+$ 274.1378, found 274.1361. Anal. Calcd for $C_{15}H_{19}N_3S$: C, 65.90; H, 7.01; N, 15.36. Found: C, 65.19; H, 7.09; N, 14.57.

4-Propylcinnolino[5,4,3][*c,d,e*][1,2]benzothiazine (13). Method A. A solution of *N*-chlorosuccinimide (0.04 g, 0.38 mmol) in dry methylene chloride (2.5 mL) was added dropwise to a solution of compound **1** (0.09 g, 0.34 mmol) in dry methylene chloride (5 mL) at − 78 °C. The stirring was continued for 2 h, during which period the mixture was gradually warmed to ambient temperature. The solution was left standing for 18 h and then refluxed for 2 h. Dilute aqueous KOH was added, and the organic layer was separated and dried (Na_2SO_4). The solvent was removed, and the residue was separated on a silica gel column. The more mobile components were removed by eluting with a benzene−EtOAc mixture (5:1 ratio) followed by elution of the product (an intense red band) with pure EtOAc to give 0.07 g (82% yield) of the product: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.94 (t, J = 7.4 Hz, 3H), 1.55−1.60 (m, 2H), 2.51 (ddd, J_1 = 7.2 Hz, J_2 = 12.7 Hz, J_3 = 8.2 Hz, 1H), 3.02 (ddd, J_1 = 6.3 Hz, J_2 = 12.5 Hz, J_3 = 8.0 Hz, 1H), 7.45 (dd, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.84 (dd, J_1 = 7.3 Hz, J_2 = 1.1 Hz, 1H), 7.98 (dd, J_1 = 8.3 Hz, J_2 = 7.4 Hz, 1H), 8.10 (dd, J_1 = 8.1 Hz, J_2 = 1.0 Hz, 1H), 8.77 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H); ^{13}C NMR (CD_2Cl_2) δ 13.4, 17.3, 54.8, 106.3, 117.1, 119.1, 119.9, 124.5, 128.0, 129.5, 132.3, 133.5, 141.8, 146.1, 146.6; IR ν_{max} 1726, 1471, 1445, 1384, 794, 712 cm^{-1}; UV (acetonitrile) λ_{max} (log ϵ) 453 (3.33), 403 (3.34), 330 (3.87), 275 (sh), 240 (4.36) and 222 (4.36) nm; HRMS (FAB$^+$) *m/z* calcd for $C_{15}H_{14}N_3S$ [M + H]$^+$ 268.0908, found 268.0912.

Method B. Compound **12** (0.21 g, 0.77 mmol) was dissolved in dry methylene chloride (5 mL), and the solution was cooled to −78 °C. Iodobenzene diacetate (0.74 g, 2.31 mmol) and anhydrous K_2CO_3 (0.77 g, 5.58 mmol) were added, and the mixture was allowed to warm gradually to ambient temperature. Stirring was continued for 12 h. The solvent was evaporated, and the residue was separated on a silica gel column by a gradual change of eluent from hexane − EtOAc (1:1 ratio) to pure EtOAc to give 0.08 g (37% yield) of the target material. NMR analysis confirmed its identity with the product from method A.

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Supporting Information Available: Tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, anisotropic thermal parameters, and crystal packing diagrams. This material is available free of charge via the Internet at http:/pubs.acs.org.

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