α-(Arylthio)imidoyl Radicals: [3 + 2] Radical Annulation of Aryl Isothiocyanates with 2-Cyano-Substituted Aryl Radicals

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A novel cascade radical reaction is described involving aryl isothiocyanates and 2-cyanoaryl radicals. The mechanism entails the formation of an α-(arylthio)imidoyl radical, a 5-exo-dig cyclization onto a cyano group, and a final 6-membered ring closure of an iminyl radical. The competitive 5-membered spiro-cyclization of the iminyl, leading to an isomeric product, was only observed in the case of a disubstituted aryl isothiocyanate. The whole process involves a rare example of [3 + 2] radical annulation and allows the one-pot synthesis of tetracondensed nitrogen heterocycles in good yields.

Introduction

Although radical chemistry was pioneered at the beginning of this century, it has not received considerable attention until the past decades, when free-radical reactions were recognized as powerful tools in organic synthesis. Over the past 20 years free radical methodology has grown more popular and now the literature displays an extraordinary number of multistep syntheses involving radicals as key intermediates.[1] In recent years, our group has drawn special attention to imidoyl radicals. These species were first studied in the late 1960s and have been generated by addition of alkyl, alkoxy, sulfanyl, silyl, or stannyl radicals to isonitriles,[2] hydrogen abstraction from imines,[3] and homolytic cleavage of suitable imidoylic precursors.[4] The reactivity of imidoyl radicals has been widely explored through fragmentation reactions,[2a−e,g,j−l,3a,j] intra-[2n,p−s,u,4a,b] and intermolecular[2m,3d,f−h,4b] additions to unsaturated bonds, and cyclizations onto aromatic rings,[3e] sulfur atoms,[3i] or cyano groups.[2t,u] Their synthetic potential has been exploited for cyclizations, annulations, and cascade reactions leading to heterocyclic compounds such as phenanthridine,[3e] quinoline,[2n,p,s,u,3d,f−g,4b] benzotriazine,[3h] indole,[2r] pyrroline,[2q] and quinoxaline[2t,u] derivatives.

A further way to generate imidoyl radicals, particularly α-thio-substituted imidoyl radicals, has involved the addition of carbon,[5] tin, or silicon[6] radicals to the sulfur atom of isothiocyanates. In principle, this procedure could prove very useful in the synthesis of heterocyclic compounds containing both a nitrogen and a sulfur atom from readily accessible starting materials. Although it has been known for a few decades, this strategy has found little application in organic synthesis. It is worth mentioning two examples, both employing stannyl or silyl radicals: the conversion of glycosyl isothiocyanates to glycosyl isonitriles and/or alditols[6f] and the synthesis of thiolactames[6g] or thiopyroglutammates[6h] by tributyltin hydride-mediated cyclization of alkenyl isothiocyanates. The latter is the only example reported in the literature concerning the synthesis of heterocyclic compounds by radical addition to isothiocyanates. Surprisingly, the addition of carbon-centered radicals is even more uncommon, the only instance being the isomerization of the

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(1) For a general view on free radicals in organic synthesis, see: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, 1986. Curran, D. P. *Synthesis* **1988**, 417 and 489. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev. (Washington, D.C.)* **1991**, *91*, 1237. Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: London, 1992. Perkins, M. J. *Radical Chemistry,* Ellis Horwood: London, 1994. Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103. Malacria, M. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 289. Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

(2) (a) Shaw, D. H.; Pritchard, H. O. *Can. J. Chem.* **1967**, *45*, 2749. (b) Saegusa, T.; Kobayashi, S.; Ito, Y.; Yasuda, N. *J. Am. Chem. Soc.* **1968**, *90*, 4182. (c) Saegusa, T.; Kobayashi, S.; Ito, Y. *J. Org. Chem.* **1970**, *35*, 2118. (d) Banks, R. E.; Haszeldine, R. N.; Stephens, C. W. *Tetrahedron Lett.* **1972**, 3699. (e) Singer, L. A.; Kim, S. S. *Tetrahedron Lett.* **1974**, 861. (f) Blum, P. M.; Roberts, B. P. *J. Chem. Soc., Chem. Commun.* **1976**, 535. (g) Kim, S. S. *Tetrahedron Lett.* **1977**, 2741. (h) Barton, D. H. R.; Bringman, G.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2665. (i) Blum, P. M.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1983**, 209. (j) Meier, M.; Rüchardt, C. *Tetrahedron Lett.* **1983**, *24*, 4671. (k) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. (l) Wirth, T.; Rüchardt, C. *Chimia* **1988**, *42*, 230. (m) Barton, D. H. R.; Ozbalik, N.; Vacher, B. *Tetrahedron* **1988**, *44*, 3501. (n) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127. (o) Diart, V.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1761. (p) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863. (q) Bachi, M. D.; Balanov, A.; Bar-Ner, N. *J. Org. Chem.* **1994**, *59*, 7752. (r) Fukuyama, T.; Xiaoqi, C.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (s) Curran, D. P.; Josien, H.; Ko, S.-B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2683. (t) Nanni, D.; Pareschi, P.; Rizzoli, C.; Sgarabotto, P.; Tundo, A. *Tetrahedron* **1995**, *51*, 9045. (u) Curran, D. P.; Liu, H.; Josien, H.; Ko, S.-B. *Tetrahedron* **1996**, *52*, 11385.

(3) (a) Ohta, H.; Tokumaru, K. *J. Chem. Soc., Chem. Commun.* **1970**, 1601. (b) Danen, W. C.; West, C. T. *J. Am. Chem. Soc.* **1973**, *95*, 6872. (c) Davies, A. G.; Nedelec, J.-Y.; Sutcliffe, R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 209. (d) Leardini, R.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1320. (e) Leardini, R.; Tundo, A.; Zanardi, G.; Pedulli, G. F. *Synthesis* **1985**, 107. (f) Leardini, R.; Nanni, D.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1591. (g) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G. *Gazz. Chim. Ital.* **1989**, *119*, 637. (h) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1989**, 757. (i) Leardini, R.; Nanni, D.; Santori, M.; Zanardi, G. *Tetrahedron* **1992**, *48*, 3961. (j) Guidotti, S.; Leardini, R.; Nanni, D.; Pareschi, P.; Zanardi, G. *Tetrahedron Lett.* **1995**, *36*, 451. (k) Leardini, R.; McNab, H.; Nanni, D. *Tetrahedron* **1995**, *51*, 12143. (l) Nanni, D.; Pareschi, P.; Tundo, A. *Tetrahedron Lett.* **1996**, *37*, 9337.

(4) (a) Bachi, M. D.; Denenmark, D. *J. Am. Chem. Soc.* **1989**, *111*, 1886. (b) Dan-oh, Y.; Matta, H.; Uemura, J.; Watanabe, H.; Uneyama, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1497.

(5) Barton, D. H. R.; Jaszberenyi, J. Cs.; Theodorakis, E. A. *Tetrahedron* **1992**, *48*, 2613.

(6) (a) Lorenz, D. H.; Becker, E. I. *J. Org. Chem.* **1963**, *28*, 1707. (b) Noltes, J. G.; Janssen, M. J. *J. Organomet. Chem.* **1964**, *1*, 365. (c) John, D. I.; Tyrrel, N. D. *J. Chem. Soc., Chem. Commun.* **1979**, 345. (d) Barton, D. H. R.; Bringmann, G.; Lamotte, G.; Motherwell, W. B.; Hay Motherwell, R. S.; Porter, A. E. A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2657. (e) John, D. I.; Tyrrell, N. D.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1981**, 901. (f) Witczak, Z. J. *Tetrahedron Lett.* **1986**, *27*, 155. (g) Bachi, M. D.; Denenmark, D. *J. Org. Chem.* **1990**, *55*, 3442. (h) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1995**, *60*, 6242. For an exhaustive discussion on the radical chemistry associated with the thiocarbonyl group, see: Crich, D.; Quintero, L. *Chem. Rev. (Washington, D.C.)* **1989**, *89*, 1413 and references therein.

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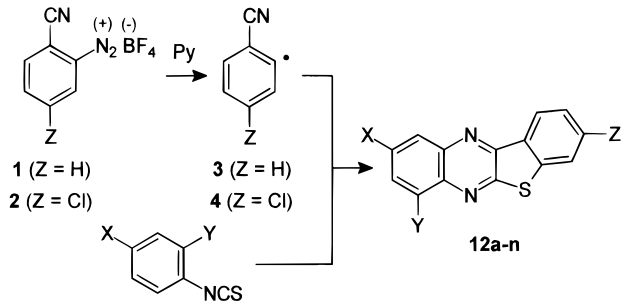
Scheme 1



5 (X = Y = H), **6** (X = Me, Y = H), **7** (X = MeO, Y = H), **8** (X = Cl, Y = H), **9** (X = Br, Y = H), **10** (X = O_2N, Y = H), **11** (X = H, Y = CN)

Table 1. Yields of Benzothienoquinoxalines 12a−n Obtained in the Reaction of Isothiocyanates 5−11 with Tetrafluoroborates 1 and 2

entry	X	Y	Z	**12** (%)
a	H	H	H	70
b	H	H	Cl	70
c	Me	H	H	57
d	Me	H	Cl	70
e	MeO	H	H	80
f	MeO	H	Cl	70
g	Cl	H	H	70
h	Cl	H	Cl	67
i	Br	H	H	57
j	Br	H	Cl	65
k	O_2N	H	H	53
l	O_2N	H	Cl	34
m	H	CN	H	65
n	H	CN	Cl	75

isothiocyanate moiety to thiocyanate group in the addition of alkyl radicals to sulfonyl isothiocyanates.[5]

Here we report a new cascade radical reaction of some aryl isothiocyanates with 2-cyanoaryl radicals. The whole sequence involves a [3 + 2] radical annulation, via an intermediate α-(arylthio)imidoyl radical, followed by cyclization of an iminyl radical. It allows the one-pot synthesis of the polycondensed framework of substituted benzothienoquinoxalines starting from commercially available or easily accessible compounds.

Results and Discussion

The aryl radicals **3** and **4** can be easily generated in pyridine at low temperature from the corresponding diazonium tetrafluoroborates **1** and **2**.[7] In a typical experiment, the aryl isothiocyanate (**5**−**11**, 15 mmol) was dissolved in pyridine; the tetrafluoroborate (5 mmol) was then added portionwise under stirring at −10 to −20 °C. After evaporation of the solvent, the residue was crystallized or chromatographed to give the benzothienoquinoxalines **12** in generally good yields (Scheme 1 and Table 1).

The reaction was sometimes affected by the low solubility of the starting aryl isothiocyanates in pyridine at low temperature. To overcome this problem, the aryl radicals were generated by an alternative method. The tetrafluoroborates **1** and **2** were decomposed in ethyl acetate at room temperature in the presence of potassium

Scheme 2

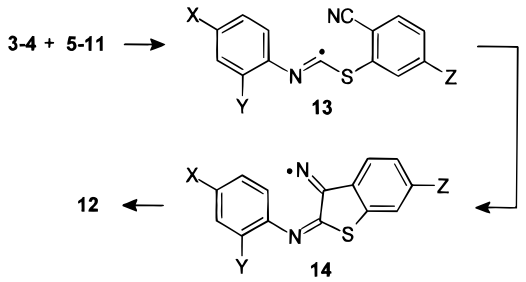


Table 2. Yields of Benzothienoquinoxalines 12c,i,k,l Obtained in the Reaction of Isothiocyanates 6, 9, and 10 with Tetrafluoroborates 1 and 2 (Crown-Ether Method)

entry	X	Y	Z	**12** (%)
c	Me	H	H	56
i	Br	H	H	77
k	O_2N	H	H	57
l	O_2N	H	Cl	69

acetate and [18-crown-6].[8] Reactions **c**, **i**, **k**, and **l** were carried out again under these conditions. The isothiocyanate (15 mmol) and the diazonium salt (5 mmol) were dissolved in ethyl acetate (20 mL) together with potassium acetate (10 mmol) and the crown ether (0.25 mmol). After 4−5 h under stirring at room temperature, the benzothienoquinoxalines **12c,i,k,l** were obtained in the yields reported in Table 2. As one can see, the modified procedure gave results comparable to (entries **c** and **k**) or significantly better (entries **i** and **l**) than the ones achieved by the pyridine method.

The reaction mechanism can be outlined as shown in Scheme 2. The aryl radical (**3**, **4**) attacks the sulfur atom of the isothiocyanate (**5**−**11**) giving the imidoyl radical **13**. Subsequent tandem 5-exo-dig cyclization of **13** onto the carbon atom of the cyano group and 6-membered ring closure of iminyl **14** onto the isothiocyanate ring afford the benzothienoquinoxaline **12**.

The intramolecular addition of a carbon radical to a cyano group is well-documented[9,2t−u] and, in the case of **13**, the 5-exo cyclization should be even more favored by the nucleophilic character of imidoyl radicals.[3g] In principle, we cannot rule out the possibility that imidoyl **13** may undergo a homolytic α-fragmentation leading to an aryl isocyanide and involving loss of a stabilized arylsulfanyl radical. Indeed, this process has been observed with α-(tributyltin)thio-[6d,f,g] and α-(triphenylmethyl)imidoyl[3l] radicals. In our case, the facile 5-exo cyclization seems to prevent the fragmentation of **13**, so that isonitriles and disulfides were detected in few cases and only in trace amounts.

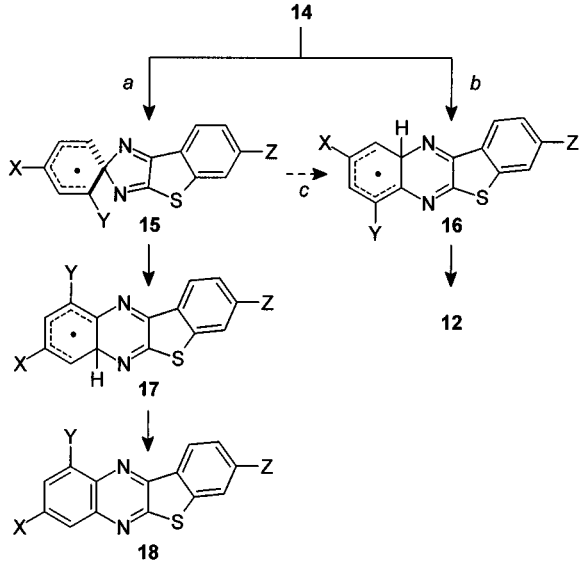
The homolytic aromatic substitution by the iminyl radical is well-precedented as well.[10] Under FVP (flash vacuum pyrolysis) conditions, iminyls are known to give rise to both 5- and 6-membered cyclizations onto aromatic

(7) Sakakura, T.; Hara, M.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1545.

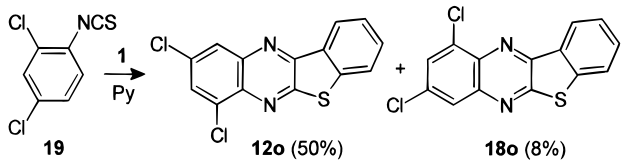
(8) Rüchardt, C.; Freudenberg, B. *Tetrahedron Lett.* **1964**, 3623. See also: Rosenberg, D. E.; Beadle, J. R.; Korzeniowski, S. H.; Gokel, G. W. *Tetrahedron Lett.* **1980**, *21*, 4141.

(9) Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313. Chenera, B.; Chuang, C. P.; Hart, D. J.; Hsu, L. Y. *J. Org. Chem.* **1985**, *50*, 5409. Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116. Beckwith, A. L. J.; O'Shea, D. M.; Sendaba, G.; Westwood, S. W. *J. Chem. Soc., Chem. Commun.* **1987**, 666. Yeung, B. W.; Contelles, J. L. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989**, 1160. Dickson, J. K., Jr.; Tsang, R.; Llera, J. M.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 5350. Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *31*, 5397. Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 322. Yang, C.-C.; Chang, H.-T.; Fang, J.-M. *J. Org. Chem.* **1993**, *58*, 3100.

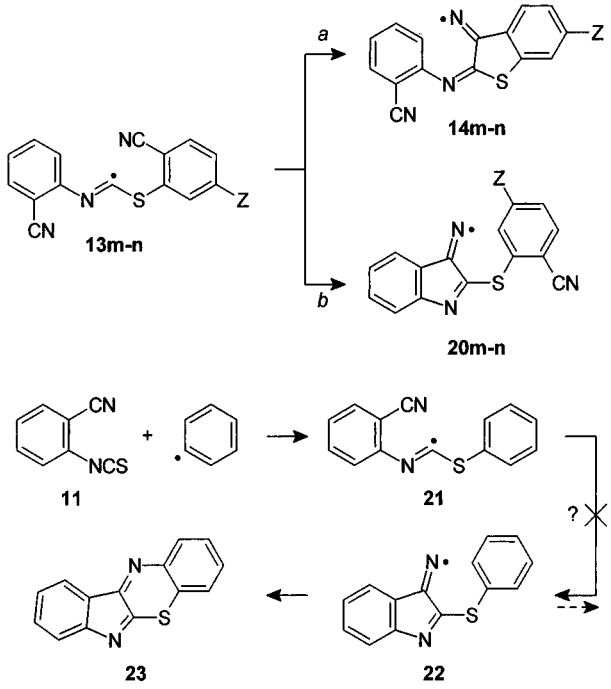
Scheme 3



Scheme 4



Scheme 5



rings,[10d−g] affording isomeric products through rearrangement of a spirocyclohexadienyl radical. In our reaction this would result in the pathway shown in Scheme 3.

On one hand, iminyl **14** can give 6-membered ring closure, leading to quinoxaline **12** through the cyclohexadienyl radical **16** (path *b*). On the other, it can undergo a competitive 5-membered *ipso*-cyclization to the spiranic intermediate **15**; rearrangement of **15** and oxidation of the cyclohexadienyl **17** eventually afford the isomeric quinoxaline **18** (path *a*).[11] Careful chromatographic and spectral analyses of the reaction mixtures showed the exclusive presence of quinoxaline **12** (see Experimental Section). This compound could also arise from radical **15** (paths *a* and *c*). Nevertheless, in our opinion, if the spirocyclohexadienyl radical is formed, it should rather rearrange by migration of either C−N bonds—giving a mixture of **12** and **18**—than afford **12** through translocation of only one C−N bond (path *c*). This let us exclude, for reactions **a**−**n**, the intervention of the intermediate **15** to a significant extent.

The feasibility of the spirocyclization was however established by the reaction of isothiocyanate **19** (Scheme 4). In this case, **19** afforded small amounts of the isomeric product **18o**, as well as major quantities of quinoxaline **12o**; **18o** can be easily accounted for through rearrangement of the spiranic radical **17o** (X = Y = Cl).

The substituents on the aromatic ring of the isothiocyanate clearly play an important role in the reaction mechanism. Both experimental and computational studies are underway to get some more information about the 1,5-spirocyclization of such iminyl radicals as **14**.[12]

Finally, it is worth pointing out that reactions **m** and **n** exclusively afforded products derived from 5-membered cyclization of the imidoyl radical on the cyano group of the diazonium salt. An analogous ring closure on the other nitrile moiety was not observed at all. This result suggests that the 5-exo-dig cyclization leading to the thiophene ring (Scheme 5, path *a*) should be highly favored compared to the similar 5-exo-dig ring closure that would afford a pyrrole ring and would be expected to occur in competition with the other one (path *b*). Actually, the reaction of isothiocyanate **11** with phenyl

(10) (a) Forrester, A. R.; Gill, M.; Thomson, R. H. *J. Chem. Soc., Chem. Commun.* **1976**, 677. (b) Sakuragi, H.; Ishikawa, S.-I.; Nishimura, T.; Yoshida, M.; Inamoto, N.; Tokumaru, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1949. (c) Forrester, A. R.; Gill, M.; Sadd, J. S.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 612. (d) McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 371. e) McNab, H.; *J. Chem. Soc., Perkin Trans. 1* **1984**, 377. (f) McNab, H.; Smith, G. S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 381. (g) Hickson, C. L.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1569.

(11) Formation and rearrangement of azaspirocyclohexadienyl radicals have been reported in the ring closure of analogous vinyl radicals: see refs 2n, 2t, 3f, and 4b.

(12) All the attempts to perform X-ray crystallographic determinations on the reaction products failed because of the unsuitable crystalline properties. Structure **12** was assigned to the products on the basis of the following arguments. It has been reported (ref 2t) that an iminyl radical very similar to **14** gives an exclusive 1,6-ring closure: in that case, the structure of the reaction product has been confirmed by X-ray diffraction. An analogous, exclusive 6-membered cyclization has been observed by Curran and co-workers (ref 2u) with an iminyl radical generated by addition of an imidoyl radical to a cyano group. Furthermore, to assign structure **18** instead of **12** to the reaction product, we have to postulate a mechanism involving exclusive spirocyclization of iminyl **14** (Scheme 3, path *a*) and one-way-rearrangement of the resulting spirocyclohexadienyl radical **15** through selective cleavage of the preexisting carbon−nitrogen bond (Scheme 3, path *c*). In our opinion, this is a very unlikely pathway. Finally, we generated radical **13e** by addition of (2-cyanophenyl)sulfanyl radical to 4-methoxyphenyl isocyanide isonitrile. The reaction afforded major amounts of quinoxaline **12e** together with traces of a crystalline byproduct derived from addition of another sulfanyl radical to **12e**. The structure of this compound was fully established by X-ray diffraction, which confirmed the expected position of the substituent on the quinoxaline ring (full details of this result will be reported elsewhere). In light of this discussion, it seems quite reasonable to assign structure **18o** to the minor product of isothiocyanate **19**. In fact, there is no reason for supposing that, also in this case, iminyl **14o** cannot give mainly 1,6-ring closure affording **12o**. The minor quantity of 5-membered cyclization, leading to the isomer **18o**, is probably the result of both a statistical factor (one of the two *ortho*-positions is not accessible for cyclization) and an increased stabilization of the spirocyclohexadienyl by the two chlorine atoms (if we postulate a reversible cyclization of **14**).

radicals gave no trace of compound **23**, yielding unreacted starting material, tars, and small amounts of diphenyl disulfide. Even assuming a reversible addition step, the 1,6-cyclization of the intermediate iminyl **22** should be sufficiently fast to drive the reaction toward the final polycyclic compound. Therefore, this result seems to indicate the complete inability of imidoyl radicals to give a pyrrole ring through 1,5-cyclization onto a cyano group.[13]

Work is in progress to obtain some quantitative data on the intermediates and transition states involved in the 5-exo-dig cyclization of imidoyl radicals to C−N triple bonds.

The addition of 2-cyanoaryl radicals to aryl isothiocyanates is a novel example of cascade radical reaction that allows the straightforward synthesis of tetracondensed heteroaromatic products starting from very simple compounds. Furthermore, reactions **a**−**n** are completely regioselective, whereas the reported synthesis of benzothienoquinoxalines starting from benzothiophene dioxide and substituted phenylenediamines always yields mixtures of isomers.[14] Our reaction is a new example of rare [3 + 2] radical annulation via α-thio-substituted imidoyl radicals. It is also the first instance of application to the synthesis of heterocyclic compounds of a radical addition, tandem cyclization strategy involving isothiocyanates and carbon-centered radicals.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform using tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were performed by electron impact with a beam energy of 70 eV: relative intensities are given in parentheses. Column chromatography was carried out on 60-Å silica gel using light petroleum ether (40−70 °C) and a light petroleum ether/diethyl ether gradient (from 0 up to 100% diethyl ether) as eluant; diethyl ether was sometimes replaced by methylene chloride. Previously reported reaction products were identified by spectral comparison and mixed melting point determination with authentic specimens.

Starting Materials. Isothiocyanates **5**−**10, 19**, 2-aminobenzonitrile, 2-amino-4-chlorobenzonitrile, thiophosgene, boron trifluoride etherate, *tert*-butyl nitrite (Aldrich), and [18-crown-6] (Merck) were commercially available. Tetrafluoroborates **1** and **2**[15] and benzo[4,5]thieno[2,3-*b*]-quinoxaline (**12a**)[16] were prepared according to the literature.

2-Isothiocyanatobenzonitrile (11).[17] A methylene chloride (25 mL) solution of 2-aminobenzonitrile (100 mmol) was added dropwise at 20 °C to a stirred solution of thiophosgene (125 mmol) in a methylene chloride (15 mL)/water (35 mL) mixture. After 3 h, methylene chloride (20 mL) was added and the organic layer was separated and dried (sodium sulfate). The solvent was evaporated and the residue was crystallized to give the title compound (80%), mp = 60−62 °C (from light petroleum ether).

General Procedure for the Reactions of the Aryl Isothiocyanates 5−11 and 19 with the Tetrafluoroborates 1 and 2. Method 1 (with Pyridine). A pyridine solution of the aryl isothiocyanate (15 mmol) was kept at −10 to −20 °C in a 50 mL round-bottomed flask under a very efficient magnetic stirring. The tetrafluoroborate (5 mmol) was then added portionwise (in ca. 1 h), keeping the temperature in the range −10 to −20 °C. The reaction mixture was warmed to room temperature, and the pyridine was evaporated. The residue was suspended in methylene chloride and filtered, and the solid was washed several times with methylene chloride. The solvent was evaporated and the residue chromatographed according to the procedure described for each compound. To exclude the presence of isomeric quinoxaline derivatives, each fraction separated by chromatography was carefully analyzed by mass spectrometry (the compounds are not suitable for GC-MS analysis). ^{1}H NMR analyses were performed on all the fractions containing the required molecular weight, and every sample (except the reaction of isothiocyanate **19**) showed perfectly identical spectra, with no extra peaks ascribable to the isomeric compounds. ^{1}H NMR spectra of the reaction crudes were also recorded. This strategy was also applied to the following methods 2 and 3.

Method 2 (with Pyridine). A pyridine solution of the aryl isothiocyanate (15 mmol) was kept at −10 to −20 °C in a 50 mL round-bottomed flask under a very efficient magnetic stirring. The tetrafluoroborate (5 mmol) was then added portionwise (in ca. 1 h), keeping the temperature in the range −10 to −20 °C. The reaction mixture was warmed to room temperature, and the pyridine was evaporated. The residue was treated with methylene chloride, which dissolved the starting aryl isothiocyanate almost exclusively. The solid, which contained most of the benzothienoquinoxaline, was washed several times with methylene chloride; the filtrates were combined, the solvent was evaporated, and the residue was chromatographed according to the procedure described in each reaction. The solid insoluble in methylene chloride was poured into water, and the resulting suspension was refluxed for a few minutes. After filtration, the residue was dissolved in hot chloroform, the solution was dried over sodium sulfate and filtered, and the solvent was evaporated. The residue was combined with the benzothienoquinoxaline previously obtained by column chromatography and crystallized.

Method 3 (with Crown Ether). [18-Crown-6] (0.25 mmol), potassium acetate (10 mmol), and the tetrafluoroborate (5 mmol) were added to an ethyl acetate (20 mL) solution of aryl isothiocyanate (15 mmol) in a 20 mL Erlenmeyer flask. The reaction mixture was kept at room temperature for 4 h under very efficient magnetic stirring. The solvent was evaporated, and the residue was suspended in methylene chloride, which dissolved the starting aryl isothiocyanate almost exclusively. The solid, which contained most of the benzothienoquinoxaline, was washed several times with methylene chloride; the filtrates were combined, the solvent was evaporated, and the residue was chromatographed according to the procedure described in each reaction. The solid insoluble in methylene chloride was poured into water, and the resulting suspension was refluxed for a few minutes. After filtration, the residue was dissolved in hot chloroform, the solution was dried over sodium sulfate and filtered, and the solvent was evaporated. The residue was combined with the benzothienoquinoxaline previously obtained by column chromatography and crystallized.

Benzo[4,5]thieno[2,3-*b*]quinoxaline (12a). According to method 1, column chromatography (light petroleum ether) gave starting phenyl isothiocyanate (**5**). Further elution with light petroleum ether/diethyl ether 50:50 v/v afforded **12a** (0.83 g, 70%): mp = 166−167 °C (from ethanol); lit.[16] mp = 166−167 °C.

3-Chlorobenzo[4,5]thieno[2,3-*b*]quinoxaline (12b). According to method 2, column chromatography (light petroleum ether) gave the starting isothiocyanate (**5**). Further elution with light petroleum ether/methylene chloride 67:33 v/v afforded **12b** (0.95 g, 70%): mp = 244−245 °C (from benzene); ^{1}H NMR (300 MHz) 7.06 (1H, dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz), 7.10 (1H, d, J = 1.7 Hz), 7.32−7.40 (2H, m), 8.11−8.18 (1H,

(13) An analogous α-phenylimidoyl radical, generated in the reaction of *N*-(phenylmethylene)-2-aminobenzonitrile with diisopropyl peroxydicarbonate (see refs 3d−k), did not afford any cyclization product either.

(14) Banerji, K. D.; Mazumdar, A. K. D.; Sen, K. K. *J. Indian Chem. Soc.* **1973**, *50*, 268.

(15) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572.

(16) Bezdrik, A.; Friedländer, P.; Koeniger, P. *Chem. Ber.* **1908**, *41*, 227.

(17) Pazdera, P.; Ondracek, D. Czech. Pat. CS 270,981, 1991; *Chem. Abstr.* **1992**, *117*, 69590u.

m), 8.21−8.30 (2H, m + d, J = 8.1 Hz); MS[18] *m/z* 272 (M^+ + 2, 37), 270 (M^+, 100), 235 (7), 135 (12); HRMS calcd for $C_{14}H_7ClN_2S$ 270.00185, found 270.0020. Anal. Calcd for $C_{14}H_7ClN_2S$: C, 62.11; H, 2.61; N, 10.35; S, 11.84. Found: C, 62.23; H, 2.61; N, 10.31; S, 11.90.

9-Methylbenzo[4,5]thieno[2,3-*b*]quinoxaline (12c). According to method 1, column chromatography (light petroleum ether) gave starting 4-methylphenyl isothiocyanate (**6**). Further elution with light petroleum ether/diethyl ether 85:15 v/v afforded **12c** (0.71 g, 57%): mp = 203−205 °C (from benzene); ^{1}H NMR (200 MHz) 2.62 (3H, s, Me), 7.52−7.71 (3H, m), 7.84−7.91 (1H, m), 8.01−8.08 (2H, m), 8.53−8.60 (1H, m); ^{13}C NMR (50 MHz) 22.5, 124.2, 124.9, 126.3, 128.4, 128.9, 131.4, 132.2, 132.8, 140.2, 140.6, 141.2, 148.3, 157.0; MS *m/z* 250 (M^+, 100), 249 (27), 125 (14); HRMS calcd for $C_{15}H_{10}N_2S$ 250.0565, found 250.0563. Anal. Calcd for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19; S, 12.81. Found: C, 72.01; H, 4.02; N, 11.17; S, 12.80.

The reaction was also carried out according to a simplified method 3: quinoxaline **12c** is soluble in methylene chloride and it can be easily obtained by extraction of the inorganic residue followed by column chromatography. Elution with light petroleum ether gave **6**; further elution with light petroleum ether/diethyl ether 85:15 v/v afforded **12c** (0.70 g, 56%); mp = 203−205 °C (from benzene).

3-Chloro-9-methylbenzo[4,5]thieno[2,3-*b*]quinoxaline (12d). According to method 2, column chromatography (light petroleum ether) gave the starting isothiocyanate **6**. Further elution with light petroleum ether/methylene chloride 67:33 v/v afforded **12d** (1.0 g, 70%): mp = 211−214 °C (from ligroin); ^{1}H NMR (200 MHz) 2.62 (3H, m, Me), 7.53 (1H, dd, J_1 = 7.9 Hz, J_2 = 1.6 Hz), 7.61−7.68 (1H, m), 7.84 (1H, d, J = 1.6 Hz), 7.98−8.06 (2H, m), 8.45 (1H, d, J = 7.9 Hz); ^{13}C NMR (75 MHz) 22.6, 124.0, 125.7, 127.1, 128.5, 128.9, 130.7, 133.1, 137.5, 140.6, 140.65, 141.3, 141.8, 147.4, 156.6; MS *m/z* 286 (M^+ + 2, 35), 284 (M^+, 100), 283 (23), 249 (4), 248 (4), 142 (10); HRMS calcd for $C_{15}H_9ClN_2S$ 284.0175, found 284.0175. Anal. Calcd for $C_{15}H_9ClN_2S$: C, 63.27; H, 3.19; N, 9.84; S, 11.26. Found: C, 63.27; H, 3.19; N, 9.85; S, 11.25.

9-Methoxybenzo[4,5]thieno[2,3-*b*]quinoxaline (12e). According to method 1, column chromatography (light petroleum ether) gave starting 4-methoxyphenyl isothiocyanate (**7**). Further elution with light petroleum ether/diethyl ether 90:10 v/v afforded **12e** (1.06 g, 80%); mp = 187−188 °C (from ethanol/chloroform); ^{1}H NMR (300 MHz) 3.40 (3H, s, OMe), 7.41 (1H, dd, J_1 = 9.1 Hz, J_2 = 2.6 Hz), 7.48 (1H, d, J = 2.6 Hz), 7.53 (1H, td, J_t = 7.5 Hz, J_d = 1.0 Hz), 7.60 (1H, td, J_t = 7.7 Hz, J_d = 1.2 Hz), 7.80−7.84 (1H, m), 7.98 (1H, d, J = 9.2 Hz), 8.46−8.51 (1H, m); ^{13}C NMR (50 MHz) 56.2, 107.1, 123.9, 124.1, 124.7, 126.1, 129.8, 131.2, 132.1, 138.3, 140.7, 142.7, 148.1, 155.2, 160.8; MS *m/z* 266 (M^+, 100), 251 (13), 223 (41), 133 (8); HRMS calcd for $C_{15}H_{10}N_2OS$ 266.0514, found 266.0512. Anal. Calcd for $C_{15}H_{10}N_2OS$ C, 67.65; H, 3.78; N, 10.52, S, 12.04. Found: C, 67.70; H, 3.77; N, 10.50; S, 12.02.

3-Chloro-9-methoxybenzo[4,5]thieno[2,3-*b*]quinoxaline (12f). According to a modified method 2, column chromatography (light petroleum ether) of the combined organic phases (methylene chloride and hot chloroform) gave the starting isothiocyanate **7**. Further elution with light petroleum ether/methylene chloride 50:50 v/v afforded **12f** (1.05 g, 70%): mp = 234−236 °C (from ethyl acetate); ^{1}H NMR (200 MHz) 4.00 (3H, s, OMe), 7.44−7.58 (3H, m), 7.85 (1H, d, J = 1.8 Hz), 8.03 (1H, dd, J_1 = 8.8 Hz, J_2 = 0.7 Hz), 8.44 (1H, d, J = 8.6 Hz); ^{13}C NMR (50 MHz) 56.6, 107.1, 124.0, 124.3, 125.5, 127.0, 129.9, 130.6, 137.4, 138.4, 141.9, 142.9, 147.3, 154.8, 161.1; MS *m/z* 302 (M^+ + 2, 37), 300 (M^+, 100), 285 (10), 257 (39), 150 (8); HRMS calcd for $C_{15}H_9ClN_2OS$ 300.0124, found 300.0125. Anal. Calcd for $C_{15}H_9ClN_2OS$: C, 59.90; H, 3.02; N, 9.31; S, 10.66. Found: C, 60.01; H, 3.03; N, 9.29; S, 10.66.

9-Chlorobenzo[4,5]thieno[2,3-*b*]quinoxaline (12 g). According to method 2, column chromatography (light petroleum ether) gave starting 4-chlorophenyl isothiocyanate (**8**). Further elution with light petroleum ether/methylene chloride 67:33 v/v afforded **12g** (0.95 g, 70%): mp = 224−226 °C (from benzene); ^{1}H NMR (300 MHz) δ 7.11−7.28 (3H, m), 7.31 (1H, dd, J_1 = 8.9 Hz, J_2 = 2.2 Hz), 7.86 (1H, d, J = 8.9 Hz), 8.29 (1H, d, J = 2.2 Hz), 8.45−8.53 (1H, m); ^{13}C NMR (75 MHz) 124.3, 125.3, 126.6, 129.1, 130.2, 131.3, 131.9, 132.0, 135.4, 140.6, 141.0, 141.5, 149.2, 158.2; MS *m/z* 272 (M^+ + 2, 37), 270 (M^+, 100), 235 (5), 135 (11); HRMS calcd for $C_{14}H_7ClN_2S$ 270.00185, found 270.0020. Anal. Calcd for $C_{14}H_7ClN_2S$: C, 62.11; H, 2.61; N, 10.35; S, 11.84. Found: C, 62.03; H, 2.61; N, 10.37; S, 11.85.

3,9-Dichlorobenzo[4,5]thieno[2,3-*b*]quinoxaline (12h). According to method 2, column chromatography (light petroleum ether) gave the starting isothiocyanate **8**. Further elution with light petroleum ether/methylene chloride 60:40 v/v afforded **12h** (1.02 g, 67%): mp = 216−218 °C (from ethyl acetate); ^{1}H NMR (200 MHz) δ 7.56 (1H, dd, J_1 = 8.5 Hz, J_2 = 1.7 Hz), 7.75 (1H, dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 7.86 (1H, d, J = 1.7 Hz), 8.08 (1H, d, J = 9.0 Hz), 8.24 (1H, d, J = 2.4 Hz), 8.45 (1H, d, J = 8.5 Hz); ^{13}C NMR (75 MHz) 124.1, 126.1, 127.4, 129.0, 130.3, 130.35, 131.6, 135.8, 138.3, 140.5, 141.6, 142.2, 148.2, 157.8; MS *m/z* 308 (M^+ + 4, 13), 306 (M^+ + 2, 69), 304 (M^+, 100), 269 (7), 234 (6), 152 (9); HRMS calcd for $C_{14}H_6Cl_2N_2S$ 303.9629, found 303.9627. Anal. Calcd for $C_{14}H_6Cl_2N_2S$: C, 55.10; H, 1.98; N, 9.18; S, 10.51. Found: C, 55.00; H, 1.98; N, 9.20; S, 10.52.

9-Bromobenzo[4,5]thieno[2,3-*b*]quinoxaline (12i). According to a simplified method 2 (the quinoxaline is not dissolved by methylene chloride during the first filtration), crystallization of the residue gave **12i** (0.89 g, 57%): mp = 237−239 °C (from benzene); ^{1}H NMR (300 MHz) δ 7.59 (1H, td, J_t = 7.7 Hz, J_d = 0.9 Hz), 7.68 (1H, td, J_t = 7.9 Hz, J_d = 1.0 Hz), 7.84−7.89 (2H, m), 8.02 (1H, d, J = 8.8 Hz), 8.45 (1H, d, J = 1.9 Hz), 8.53−8.58 (1H, m); ^{13}C NMR (75 MHz) 123.5, 124.3, 125.4, 126.6, 130.3, 131.9, 132.1, 132.5, 133.8, 140.8, 141.0, 141.8, 149.1, 158.5; MS *m/z* 316 (M^+ + 2, 100), 314 (M^+, 93), 235 (15), 158 (9); HRMS calcd for $C_{14}H_7BrN_2S$ 313.9513, found 313.9513. Anal. Calcd for $C_{14}H_7BrN_2S$: C, 53.35; H, 2.24; N, 8.89; S, 10.17. Found: C, 53.31; H, 2.24; N, 8.91; S, 10.19.

The reaction was also carried out according to a simplified method 3: quinoxaline **12i** is completely insoluble in methylene chloride and can be easily obtained by crystallization of the residue of the first filtration. We obtained 1.21 g (77%) of **12i**; mp = 237−239 °C (from benzene).

9-Bromo-3-chlorobenzo[4,5]thieno[2,3-*b*]quinoxaline (12j). According to method 2, column chromatography (light petroleum ether) gave the starting isothiocyanate **9**. Further elution with light petroleum ether/methylene chloride 40:60 v/v afforded **12j** (1.13 g, 65%): mp = 218−220 °C (from ethyl acetate); ^{1}H NMR (300 MHz) δ 7.56 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 7.84−7.91 (2H, dd + d, J_{1dd} = 8.9 Hz, J_{2dd} = 2.0 Hz, J_d = 1.6 Hz), 8.01 (1H, d, J = 8.9 Hz), 8.41−8.47 (2H, d + d, J = 2.0 Hz, J = 8.3 Hz); MS *m/z* 352 (M^+ + 4, 28), 350 (M^+ + 2, 100), 348 (M^+, 80), 269 (10), 234 (7), 175 (9), 174 (6); HRMS calcd for $C_{14}H_6BrClN_2S$ 347.9124, found 347.9122. Anal. Calcd for $C_{14}H_6BrClN_2S$: C, 48.09; H, 1.73; N, 8.01; S, 9.17. Found: C, 47.99; H, 1.73; N, 7.99; S, 9.19.

9-Nitrobenzo[4,5]thieno[2,3-*b*]quinoxaline (12k). According to method 2, column chromatography (light petroleum ether/methylene chloride 70:30 v/v) gave starting 4-nitrophenyl isothiocyanate (**10**). Further elution with light petroleum ether/methylene chloride 50:50 v/v afforded **12k** (0.74 g, 53%): mp = 267−269 °C (from dioxane/benzene); ^{1}H NMR (200 MHz) δ 7.65 (1H, td, J_t = 7.6 Hz, J_d = 0.9 Hz), 7.75 (1H, td, J_t = 7.6 Hz, J_d = 1.3 Hz), 7.88−7.95 (1H, m), 8.29 (1H, d, J = 9.3 Hz), 8.57 (1H, dd, J_1 = 9.3 Hz, J_2 = 2.5 Hz), 8.59−8.66 (1H, m), 9.20 (1H, d, J = 2.5 Hz); MS *m/z* 281 (M^+, 100), 251 (5), 235 (46), 223 (16), 140 (2); HRMS calcd for $C_{14}H_7N_3O_2S$ 281.0259, found 281.0259. Anal. Calcd for $C_{14}H_7N_3O_2S$: C, 59.78; H, 2.51; N, 14.94; S, 11.40. Found: C, 59.85; H, 2.51; N, 14.97; S, 11.38.

The reaction was also carried out according to method 3: column chromatography (light petroleum ether/methylene

(18) All of the mass spectra of the benzothienoquinoxalines with even M^+ show peaks corresponding to $m/z = M^+/2$, whereas the benzothienoquinoxalines with odd M^+ are characterized by peaks at $m/z = M^+/2 \pm 0.5$. This is probably due to double-charged molecular ions. See also: Pring, B. G.; Stjernström, N. E. *Acta Chem. Scand.* **1968**, *22*, 549.

chloride 50:50 v/v) gave 0.80 g (57%) of quinoxaline **12k**; mp 267−269 °C (from dioxane/benzene).

3-Chloro-9-nitrobenzo[4,5]thieno[2,3-*b*]quinoxaline (12l). According to method 2, column chromatography (light petroleum ether/methylene chloride 70:30 v/v) gave the starting isothiocyanate **10**. Further elution with light petroleum ether/methylene chloride 50:50 v/v afforded **12l** (0.53 g, 34%): mp = 250−252 °C (from benzene); ^{1}H NMR (200 MHz) δ 7.61 (1H, dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 7.90 (1H, d, J = 1.5 Hz), 8.28 (1H, d, J = 8.9 Hz), 8.51 (1H, d, J = 8.1 Hz), 8.58 (1H, dd, J_1 = 8.9 Hz, J_2 = 2.3 Hz), 9.16 (1H, d, J = 2.3 Hz); MS *m*/*z* 317 (M^+ + 2, 33), 315 (M^+, 100), 285 (3), 271 (16), 269 (44), 259 (6), 257 (14), 234 (12), 157 (7); HRMS calcd for $C_{14}H_6ClN_3O_2S$ 314.9869, found 314.9870. Anal. Calcd for $C_{14}H_6ClN_3O_2S$: C, 53.26; H, 1.92; N, 13.31; S, 10.16. Found: C, 53.17; H, 1.92; N, 13.33; S, 10.17.

The reaction was also carried out according to method 3: column chromatography (light petroleum ether/methylene chloride 50:50 v/v) gave 1.09 g (69%) of quinoxaline **12l**.

Benzo[4,5]thieno[2,3-*b*]quinoxaline-7-carbonitrile (12m). According to a modified method 2, column chromatography (light petroleum ether/methylene chloride 80:20 v/v) of the combined organic phases (methylene chloride and hot chloroform) gave starting 2-isothiocyanatobenzonitrile (**11**). Further elution with light petroleum ether/methylene chloride 60:40 v/v afforded **12m** (0.85 g, 65%): mp = 264−265 °C (from ethyl acetate); ^{1}H NMR (300 MHz) δ 7.63 (1H, ddd, J_1 = 7.8 Hz, J_2 = 7.3 Hz, J_3 = 0.9 Hz), 7.74 (1H, ddd, J_1 = 8.0 Hz, J_2 = 7.3 Hz, J_3 = 1.2 Hz), 7.86 (1H, dd, J_1 = 8.5 Hz, J_2 = 7.3 Hz), 7.91−7.95 (1H, m), 8.22 (1H, dd, J_1 = 7.3 Hz, J_2 = 1.2 Hz), 8.52 (1H, dd, J_1 = 8.5 Hz, J_2 = 1.2 Hz), 8.57−8.62 (1H, m); MS *m*/*z* 261 (M^+, 100), 234 (3), 131 (12); HRMS calcd for $C_{15}H_7N_3S$ 261.0361, found 261.0360. Anal. Calcd for $C_{15}H_7N_3S$: C, 68.95; H, 2.70; N, 16.08; S, 12.27. Found: C, 69.10; H, 2.70; N, 16.01; S, 12.28.

3-Chlorobenzo[4,5]thieno[2,3-*b*]quinoxaline-7-carbonitrile (12n). According to method 2, column chromatography (light petroleum ether/methylene chloride 80:20 v/v) gave the starting isothiocyanate **11**. Further elution with light petroleum ether/methylene chloride 60:40 v/v afforded **12n** (1.11 g, 75%): mp = 302−304 °C (from benzene); ^{1}H NMR (300 MHz) δ 7.61 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.88 (1H, dd, J_1 = 8.4 Hz, J_2 = 7.1 Hz), 7.93 (1H, d, J = 1.8 Hz), 8.23 (1H, dd, J_1 = 7.1 Hz, J_2 = 1.2 Hz), 8.49−8.54 (2H, m); MS *m*/*z* 297 (M^+ + 2, 42), 295 (M^+, 100), 260 (3), 147 (8); HRMS calcd for $C_{15}H_6ClN_3S$ 294.9971, found 294.9972. Anal. Calcd for $C_{15}H_6ClN_3S$: C, 60.92; H, 2.04; N, 14.21; S, 10.84. Found: C, 61.00; H, 2.04; N, 14.18; S, 10.84.

7,9-Dichlorobenzo[4,5]thieno[2,3-*b*]quinoxaline (12o) and 8,10-dichlorobenzo[4,5]thieno-[2,3-*b*]quinoxaline (18o). According to method 2, column chromatography (light petroleum ether/diethyl ether 90:10 v/v) gave starting 2,4-dichlorophenyl isothiocyanate (**19**). Further elution with light petroleum ether/diethyl ether 60:40 v/v afforded **12o** (0.76 g, 50%), mp = 231−233 °C (from benzene) [^{1}H NMR (200 MHz) δ 7.00−7.19 (3H, m), 7.44 (1H, d, J = 2.0 Hz), 8.04 (1H, d, J = 2.0 Hz), 8.34−8.43 (1H, m); MS *m*/*z* 308 (M^+ + 4, 12), 306 (M^+ + 2, 65), 304 (M^+, 100), 269 (3), 234 (5), 152 (10), 108 (7); HRMS calcd for $C_{14}H_6Cl_2N_2S$ 303.9629, found 303.9621. Anal. Calcd for $C_{14}H_6Cl_2N_2S$: C, 55.10; H, 1.98; N, 9.18; S, 10.51. Found: C, 55.30; H, 1.99; N, 9.22; S, 10.46], and **18o** (0.12 g, 8%), mp = 255−257 °C (from benzene) [^{1}H NMR (200 MHz) δ 7.15−7.30 (1H, m), 7.50−7.95 (3H, m + d, J = 1.9 Hz), 8.08 (1H, d, J = 1.9 Hz), 8.55−8.70 (1H, m); MS *m*/*z* 308 (M^+ + 4, 13), 306 (M^+ + 2, 67), 304 (M^+, 100), 269 (3), 234 (7), 152 (11), 108 (10); HRMS calcd for $C_{14}H_6Cl_2N_2S$ 303.9629, found 303.9623. Anal. Calcd for $C_{14}H_6Cl_2N_2S$: C, 55.10; H, 1.98; N, 9.18; S, 10.51. Found: C, 55.28; H, 1.99; N, 9.23; S, 10.47].

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