Cascade Radical Reaction of 2-Alkynyl-Substituted Aryl Radicals with Aryl Isothiocyanates: A Novel Entry to Benzothieno[2,3-*b*]quinolines through α-(Arylsulfanyl)imidoyl Radicals

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The novel cascade radical reaction of 2-(phenylalkynyl)aryl radicals with 4-Y-phenyl isothiocyanates (Y = H, OMe, Me, Cl, CN) provides a useful one-pot protocol for the production of 8-Y-substituted (**12**) and/or 9-Y-substituted benzothieno[2,3-*b*]quinolines (**11**). The whole process entails primary formation of an α-(2-alkynylarylsulfanyl)imidoyl radical that undergoes smooth 5-exo-dig cyclization onto the alkynyl triple bond. The derived 1-phenylvinyl radical then exhibits six-membered cyclization onto the isothiocyanate ring, to give **11**, and/or five-membered ipso-cyclization to an azaspiro intermediate, whose eventual rearrangement affords **12**. The overall findings clearly showed that the relative proportion of the outcoming isomeric benzothienoquinolines **11** and **12** can be markedly affected by the nature of the original isothiocyanate substituent. Moreover, the findings also furnished the first chemical evidence that enhancing the electrophilic power of the employed radical can properly enhance the reactivity of aryl radicals toward isothiocyanates.

Introduction

Imidoyl radicals are attractive reactive intermediates that can be readily produced by addition of carbon- and heteroatom-centered radicals to isonitriles,[1] by hydrogen atom abstraction from imines,[2] as well as by homolytic fragmentation of certain imidoylic precursors.[3] In recent years the synthetic potential of these radical species has been widely exploited in cyclizations, annulations, and cascade reactions, leading to the construction of various heterocyclic nitrogen-containing compounds, including phenanthridines,[2e] quinolines,[4,2d,f,g] indoles,[5] benzotriazines,[2h] and quinoxalines.[4c,6] The α-sulfanyl-substituted species have so far found only little use in organic synthesis. However, since the early 1960s the reported studies have clearly revealed that this type of imidoyl radical is smoothly formed upon addition of carbon[7] and, especially, tin and silicon[8] radicals to the sulfur atom of accessible isothiocyanates. Only quite recently the reaction of carbon-centered radicals with isothiocyanates has been shown to be synthetically appealing. In fact, in 1992 the reaction of alkyl radicals with sulfonyl isothiocyanates was reported by Barton and co-workers[7] to result in practicable isomerization of the isothiocyanate moiety to the thiocyanate group via transient α-(alkylsulfanyl)-imidoyl radical adducts. Moreover, in 1997 we reported a novel radical cascade reaction that involves 2-cyanoaryl radicals and aryl isothiocyanates and allows the one-pot synthesis of substituted benzothienoquinoxalines from commercially available or easily accessible materials.[9] The whole process entailed the initial formation of an α-(2-cyanoarylsulfanyl)imidoyl radical,[10] followed by a 5-exo-dig cyclization onto the cyano group and a final six-membered ring cyclization of the ensuing iminyl radical

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(10) Analogous α-(2-cyanophenylsulfanyl)-substituted imidoyl radicals have been subsequently produced through addition of 2-cyanophenylsulfanyl radical to aromatic isonitriles; see ref 1b.

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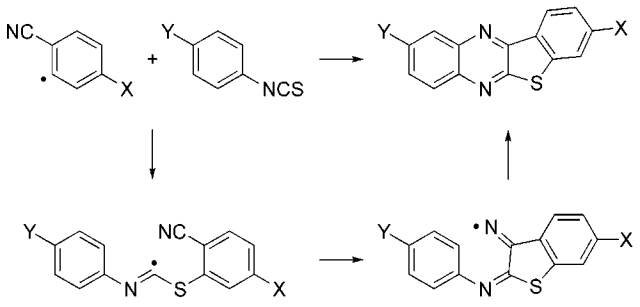
Scheme 1. Reaction of 2-Cyanoaryl Radicals with Aryl Isothiocyanates



X = H, Cl; Y = H, OMe, Me, Cl, Br, NO_2

onto the aromatic ring of the original isothiocyanate (Scheme 1).

In view of our long interest in the chemical reactivity and utility of imidoyl radicals,[1,2d−l,9] we were next prompted to search for a further synthetic use for the α-sulfanylated members by examining related addition reactions of 2-alkynylaryl radicals with aryl isothiocyanates. We considered that derived α-(2-alkynylarylsulfanyl)imidoyl radicals might usefully lead to (virtually unknown) benzothieno[2,3-*b*]quinolines[11] through a mechanistic route similar to that we had discovered for the α-(2-cyanoarylsulfanyl)-substituted analogues. Herein we report our successful results from a study of the reactions of the 2-(phenylethynyl)phenyl radical **3** and its 4-cyano derivative **4** with some aryl isothiocyanates **5**−**9**, as shown in Scheme 2.

Results and Discussion

Following our previous procedure employed for corresponding reactions of 2-cyanoaryl radicals,[9] the aryl radical **3** was readily generated upon portionwise addition of the diazonium tetrafluoroborate (**1**, 5 mmol) to a stirred pyridine solution of the appropriate isothiocyanate (**5**−**9**, 15 mmol) being carefully kept below 0 °C. After the suitable time, the crude reaction mixture was normally subjected to chromatographic separation. With the parent isothiocyanate **5**, a satisfactory yield of the desired 11-phenylbenzothienoquinoline **11a** could be obtained (Scheme 2 and Table 1, entry 1). With 4-methoxyphenyl isothiocyanate **6**, the 9-methoxy-substituted derivative **11b** was similarly obtained as a single quinoline compound, albeit in a somewhat lower yield (Scheme 2 and Table 1, entry 2). Moreover, with 4-methyl- (**7**) and 4-chlorophenyl isothiocyanate (**8**), the respective 9-substituted benzothienoquinolines **11c**−**d** were also successfully formed to a comparable extent. However, under these circumstances minor amounts of the isomeric 8-substituted compounds **12c**−**d** were additionally produced in a relative proportion increasing on passing from the isothiocyanate **7** to **8** (Scheme 2 and Table 1, entries 3−4). Instead, in the case of 4-cyanophenyl isothiocyanate **9**, no proof for any occurrence of quinoline product **11e** or **12e** was obtained after usual chromatography of the (especially complex) reaction mixture (Scheme 2 and Table 1, entry 5).

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Scheme 2. Reaction of 2-Ethynylaryl Radicals with Aryl Isothiocyanates

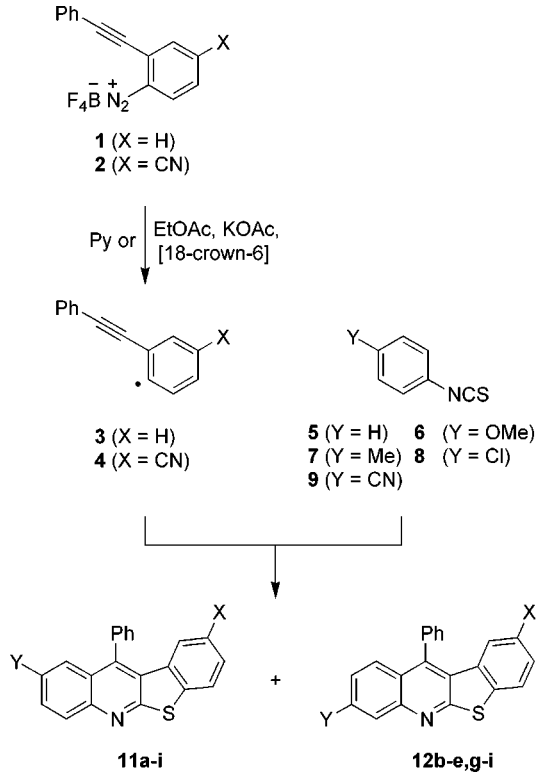


Table 1. Yields[a] of Benzothienoquinolines 11 and 12 from the Reaction of Isothiocyanates 5−9 with Tetrafluoroborates 1 and 2 in Pyridine

entry	X	Y	**11** (%)	**12** (%)
1	H	H	**11a** (50)	
2	H	OMe	**11b** (39)	**12b** (−)
3	H	Me	**11c** (30)	**12c** (6)
4	H	Cl	**11d** (33)	**12d** (11)
5	H	CN	**11e** (−)	**12e** (−)
6	CN	H	**11f** (60)	
7	CN	OMe	**11g** (52)	**12g** (−)
8	CN	Cl	**11h** (40)	**12h** (16)
9	CN	CN	**11i** (12)	**12i** (21)

[a] Yields are for the pure compounds obtained after column chromatography.

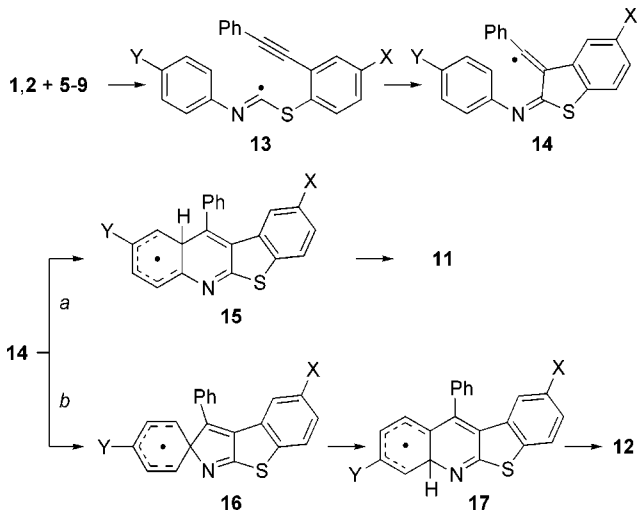
Since our previous study had revealed that the reaction of 2-cyanoaryl radicals with isothiocyanates can be carried out also in ethyl acetate with comparable or even better results than in pyridine,[9] we were led to further explore the reaction of radical **3** with the compounds **7**−**9** by achieving homolytic decomposition of the tetrafluoroborate **1** in ethyl acetate. To this purpose, the tetrafluoroborate **1** was treated with a 3-fold excess of isothiocyanate in ethyl acetate in the presence of potassium acetate and [18-crown-6] at room temperature.[9] Under these conditions, isothiocyanates **7** and **8** furnished isomeric mixtures of quinolines **11c**,**d** and **12c**,**d** in somewhat higher and lesser overall yields, respectively, than those achieved by the pyridine method (Table 2, entries 1 and 2). In the case of **8**, the diminished occurrence of the isomers **11d** and **12d** was probably due to concomitant production of tolane, arising from unfavorable reaction of the radical **3** with the hydrogen donor solvent. More interestingly, under those circumstances even 4-cyanophenyl isothiocyanate **9** successfully furnished practicable amounts of a corresponding mixture of **11e** and **12e**; in this case, however, the 8-cyano-

Table 2. Yields[a] of Benzothienoquinolines 11 and 12 from the Reaction of Isothiocyanates 7−9 with Tetrafluoroborates 1 and 2 in Ethyl Acetate (crown ether method)

entry	X	Y	**11** (%)	**12** (%)
1	H	Me	**11c** (45)	**12c** (9)
2	H	Cl	**11d** (27)	**12d** (9)
3	H	CN	**11e** (7)	**12e** (13)
4	CN	CN	**11i** (12)	**12i** (19)

[a] Yields are for the pure compounds obtained after column chromatography.

Scheme 3. Reaction Mechanism for the Formation of Isomeric Quinolines 11 and 12



substituted isomer **12e** unusually occurred as the major component (Table 2, entry 3).

Thus, the above findings clearly showed that the α-sulfanylimidoyl radical **13**, as formed upon attack of the radical **3** on the sulfur atom of **5**−**9**, can smoothly undergo 5-exo-dig cyclization onto the adjacent ethynyl moiety to give a linear 1-phenylvinyl radical **14** (Scheme 3).[13] The (intermolecular) addition of certain imidoyl radicals to alkynes is precedented.[2d,f,g] In the case of **13** the "facile" intramolecular addition to the C−C triple bond seemed to prevent alternative α-fragmentation, which in principle might result in loss of arylsulfanyl radical and concomitant occurrence of aryl isocyanide.[9,1b]

The derived vinyl radical **14** can hence undergo intramolecular six-membered cyclization onto the isothiocyanate ring, leading to the benzothienoquinoline **11** through the cyclohexadienyl radical **15** (Scheme 3, path a). The radical **14** can additionally undergo a competing five-membered ipso-cyclization to the spiranic intermediate **16**, whose subsequent rearrangement to **17** through migration of the C−N bond eventually affords the isomeric quinoline **12** (Scheme 3, path b). Intramolecular vinyl radical cyclizations onto aromatic rings are well-documented,[2d,f,g,14] and there are several instances of formation and rearrangement of analogous azaspirocyclohexadienyl radical intermediates.[2f,3b,6]

It is worth noting that in previous intramolecular cyclizations to quinolines some related 1-phenylvinyl radicals seemed to exhibit a preference for forming spiro intermediates of type **16**.[2f,15] By contrast, the present radicals **14** were found to exhibit a tendency to form the six-membered intermediates **15**, although to an extent strongly dependent upon the aromatic Y-substituent (Table 1, entries 2−4, and Table 2, entries 1−3).

It is not easy to figure out how to explain this behavior, in which stereoelectronic and polar effects can jointly play an important role. Semiempirical calculations performed on radicals **15a**,**b**,**e** and **16a**,**b**,**e** and the transition states connecting **14a**,**b**,**e** with **15a**,**b**,**e** and **14a**,**b**,**e** with **16a**,**b**,**e** showed that the six-membered cyclization is largely preferred over the 1,5-ring closure both from a thermodynamic and a kinetic point of view. Actually, the calculated energy and activation-barrier differences (ca. 20 and 4 kcal/mol, respectively) for the two competitive pathways are too large to account for the occurrence of the 1,5-cyclization process to a significant extent. Furthermore, the dependence of the same quantities on the nature of the Y-substituent was found to be negligible (Table 3; for the geometries of radicals **14a**,**b**,**e**, **15a**,**b**,**e**, and **16a**,**b**,**e** and the corresponding transition states, see the Supporting Information). On the other hand, calculations suggest that the preference observed for 1,5-ring closure when Y = CN cannot be ascribed to additional delocalization, since the methoxy group was predicted to favor the spirocyclization to a comparable extent. Since it is known that radical addition to aromatic systems can also be governed by polar effects (see ref 14 and references therein), we calculated the charge distribution in the starting vinyl radicals **14a**−**e**. All of these intermediates show comparable negative charges on the vinylic carbon, whereas the aromatic carbon atom linked to the nitrogen exhibits a positive charge density that gradually increases on passing from radical **b** to radicals **c**, **d**, and **e**, and it is well-correlated to the decrease in the **11**/**12** ratio (Table 4; see also entries 2−4 of Table 1 and entry 3 of Table 2). It therefore appears that our vinyl radicals **14**, contrary to other vinyl radicals,[14] possess a slightly nucleophilic character. The negative density on the vinylic carbon, and hence its nucleophilicity, is probably the result of a conjugative balance between the negatively charged nitrogen (ca. −0.2) and the positive sulfur (ca. 0.3), which produces a negative charge density on the aryl ring linked to the sulfur atom. The nearly isoenthalpic spirocyclization of **14** onto the *N*-aryl ring could hence be SOMO/LUMO controlled and therefore significantly affected by the Y-substituent. On the contrary, the highly exothermic 1,6-cyclization could be dominated by enthalpic factors, with neither polar nor stabilization effects playing important roles. More data are however definitely to be acquired before attempting a sound, full explanation of the final cyclization step.

The present addition of 2-(phenylethynyl)phenyl radical **3** to the aryl isothiocyanates **5**−**9** therefore provided a further interesting example of a cascade radical reaction that could involve the primary intervention of sulfanylimidoyl radical **13** and could allow the one-pot construction of the substituted benzothienoquinolines **11** and **12**. However, compared to the corresponding addi-

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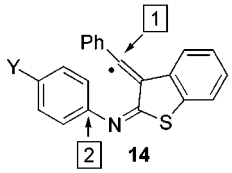
(14) Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1998**, *63*, 537.

(15) Quinolines are found to occur upon intramolecular cyclization of certain 1-phenylvinyl radicals arising from addition of *N*-arylimidoyl radicals to phenylacetylene; see ref 2f.

Table 3. Calculated Energies and Activation Barriers (MNDO-d) for Radicals 14a,b,e, 15a,b,e, and 16a,b,e, and the Transition States Connecting 14 with 15 and 14 with 16 (values in Kcal/mol)

entry	Y	**14**	**15**	**16**	E_a (**14**−**15**)	E_a (**14**−**16**)	Δ16/**15**	ΔE_a (**14**−**15**)/ E_a (**14**−**16**)
a	H	132.7	111.1	132.1	18.3	23.0	21.0	4.7
b	OMe	92.7	71.7	91.7	18.5	22.9	20.0	4.4
e	CN	163.0	142.4	162.3	18.8	23.1	19.9	4.3

Table 4. Calculated Charge Densities (MNDO-d) for the Radical Center (d_1) and the *C*-N Aromatic Carbon (d_2) for Vinyl Radicals 14a−e



entry	Y	d_1	d_2	11/12
a	H	0.110	0.024	∞
b	OMe	0.110	0.022	∞
c	Me	0.110	0.027	5
d	Cl	0.111	0.031	3
e	CN	0.111	0.044	0.5

tions of 2-cyanoaryl radicals, which normally afford benzothienoquinoxalines in good yields,[9] the reactions of **3** were found to be somewhat less rewarding, since they often led to the ultimate quinoline products in modest or even poor yields. This fact was believed to be a major consequence of the relatively modest reactivity of 2-alkynylphenyl radical **3** toward isothiocyanate substrates. Indeed, compared to a 2-cyanoaryl congener, the radical **3** might plausibly be less capable of attacking a fairly nucleophilic isothiocyanate sulfur, owing to its predictably less electrophilic nature. To clarify this point, we subsequently performed a brief comparative study of the behavior of the 4-cyanoaryl radical **4** with the isothiocyanates **5**, **6**, **8**, and **9**. Like **3**, the 4-cyano derivative **4** was generated by the homolytic decomposition of the available tetrafluoroborate **2** using the crown ether and/or the pyridine method. As can be seen in Table 1 (entries 6−9) and in Table 2 (entry 4), in all the examined cases the radical **4** gave rise to noticeably better yields of benzothienoquinoline products than those furnished by **3**. In light of the general evidence provided by the present (and previous) findings, it may be therefore inferred that the reactivity of an aryl radical with an isothiocyanate—and hence the efficiency of the resulting cascade radical reaction— can be properly enhanced by enhancing the electrophilic character of the starting radical.[16]

All the newly prepared benzothienoquinolines **11a**−**i** and **12c**−**e**,**h**,**i** were identified on the basis of ^{1}H and ^{13}C NMR and MS spectral data in addition to elemental analysis. In particular, structural assignment of the 9-substituted and 8-substituted positional isomers, **11c**−**e**,**h**,**i** and **12c**−**e**,**h**,**i**, was essentially based on the observed value of the (ortho- or meta-like) coupling constant exhibited by the proton attached at the 7-position, whose absorption was normally assumed to occur at the lowest field. This assumption was dictated by the known fact that the 8-proton of a quinoline ring (the analogous of the 7-proton of **11** or **12**) usually absorbs at lower field than the protons at the 5-, 6-, and 7-positions, in addition to the fact that a quinoline 8-proton is expected to absorb at lower field than any proton attached to the benzene moiety of a benzothiophene ring (Figure 1).[12]

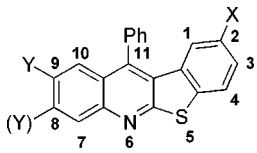


Figure 1. Atom numbering scheme of the benzothieno[2,3-*b*]quinoline [**11** or (**12**)] skeleton.

In search for further support for the reliability of the above structural assignments, we were led to perform NOE experiments with the 2-cyano-substituted benzothienoquinolines **11h** and **12i**, which had respectively a chloro atom in the 9-position and a cyano group in the 8-position. The choice of those two compounds arose from the fact that their ^{1}H NMR spectra, besides showing distinct signals due to the "quinoline" and "benzothiophene" protons, also showed two distinct multiplets each, respectively due to the two ortho protons and the four para and meta protons of the phenylic 11-substituent. We considered that irradiation of the ortho phenylic protons of **11h** and **12i** might cause some enhancement of the corresponding signals of the H-10 (and H-1) benzothienoquinoline protons. This fact might then allow to us establish the absorption of the respective 10-proton and hence the respective coupling constant, whose value was expected to be consistent with meta coupling in the case of **11h** and with ortho coupling in the case of **12i**. Irradiation of the ortho phenylic protons of **11h** at δ ∼7.40 actually caused ∼4.5% enhancement of two doublets at δ 6.94 (J = 1.5 Hz) and δ 7.61 (J = 2.2 Hz); these were consequently ascribed to the H-1 and H-10 benzothienoquinoline protons, respectively. In view of the meta coupling displayed by the H-10 signal, the original structure **11h** was therefore confirmed. The subsequent findings obtained from analogous NOE experiment with the compound **12i** also provided confirmation of this latter proposed structure (see the Supporting Information).

Conclusions

In this work we have devised a novel protocol for the one-pot construction of benzothieno[2,3-*b*]quinolines, for whose *b*-fused quinoline structure, surprisingly, literature examples are almost totally absent.[11] Our protocol is based on a radical cascade reaction that entails a rare [3 + 2] annulation[17] and is initiated by a still uncommon addition of an aryl radical to an isothiocyanate. The reaction yields two isomeric quinoline derivatives arising through competitive six- or five-membered cyclization of

(16) Evidence that the reactivity of aryl radicals depends on ring substitution has already been reported; see, for instance: Hey, D. H. *Adv. Free Radical Chem.* **1967**, *2*, 47.

(17) For [3 + 2] radical annulations, see ref 9 and (a) Albertazzi, A.; Leardini, R.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Org. Chem.*, **1984**, *49*, 4482. (b) Leardini, R.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1390. (c) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G. *Tetrahedron Lett.* **1998**, *39*, 2441.

the final vinyl radical. The isomer ratio seems to be dependent on the nature of the Y-substituent. Apparently, the "rearranged" isomer becomes more and more favored by increasing the electron-withdrawing capability of the substituent of the aryl ring involved in the cyclization, probably as a result of a SOMO/LUMO controlled cyclization of a slightly nucleophilic vinyl radical. We found evidence that also the attack of the aryl radical on the isothiocyanate is affected by polar factors: substituents that increase the electrophilicity of the aryl radical seem to favor addition to the substantially nucleophilic sulfur atom of the isothiocyanate, hence increasing the overall efficiency of the cascade reaction. Finally, since these reactions involve α-(arylsulfanyl)imidoyl radicals as key intermediates, the versatile potential of imidoyl radical chemistry in heterocyclic synthesis has been further enlarged.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform using tetramethylsilane as an internal standard. Mass spectra (MS) were performed by electron impact with a beam energy of 70 eV; relative intensities are given in parentheses. Column chromatography was carried out on ICN silica gel (63−200, 60 Å) by gradual elution with light petroleum (40−70 °C)/diethyl ether mixtures (from 0 up to 100% diethyl ether); diethyl ether eluant was sometimes replaced by methylene chloride.

Starting Materials. Isothiocyanates **5**−**8** and [18-crown-6] (Merck) were commercially available. 4-Isothiocyanatobenzonitrile **9**, mp 120−121 °C, was prepared in 50% yield by reacting 4-aminobenzonitrile with thiophosgene in dichloromethane/water.[18] Tetrafluoroborates **1** and **2** were prepared according to the literature.[19]

General Procedure for the Reactions of the Aryl Isothiocyanates 5−9 with the Tetrafluoroborates 1 and 2. Method 1 (with Pyridine). The tetrafluoroborate (5 mmol) was added portionwise (over ca. 1 h) to a vigorously stirred solution of the aryl isothiocyanate (15 mmol) in pyridine (20−30 mL), kept at −10 to −20 °C in a 50 mL round-bottomed flask. The reaction mixture was warmed to room temperature and the pyridine was then 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. Yields of the benzothienoquinolines **11a**-**d**,**f**−**i** and **12b**−**d**,**g**−**i**, as obtained by this method, are given in Table 1. ^{1}H NMR, ^{13}C NMR, and MS spectra of compounds **11** and **12** (except **11a**) are reported in the Supporting Information.

Method 2 (with Crown Ether). [18-Crown-6] (0.25 mmol), potassium acetate (10 mmol), and the tetrafluoroborate (5 mmol) were added to a solution of aryl isothiocyanate (15 mmol) in 20 mL of ethyl acetate. The reaction mixture was kept at room temperature for ca. 24 h under vigorous stirring and was then filtered. The filtrate was evaporated and the residue eventually chromatographed. Yields of the benzothienoquinolines **11c**,**d**,**e**,**i** and **12c**,**d**,**e**,**i**, as obtained by this method, are shown in Table 2.

Reaction of Isothiocyanate 5 with Tetrafluoroborate 1. Following method 1, column chromatography (light petroleum) gave unreacted phenyl isothiocyanate (**5**). Further elution with light petroleum/diethyl ether 80:20 v/v afforded 11-phenyl[1]benzothieno[2,3-*b*]quinoline (**11a**): mp 175−177 °C (from light petroleum/benzene); ^{1}H NMR (200 MHz) δ 6.76 (1 H, bd, J = 8.0 Hz), 7.05 (1 H, ddd, $J_1 = J_2 = 8.0$ Hz, $J_3 = 0.8$ Hz), 7.30−7.46 (4 H, m), 7.55−7.79 (6 H, m), 8.16 (1 H, bd, J = 8.5 Hz); ^{13}C NMR (75 MHz) δ 122.87, 124.59, 125.37, 125,43, 125.87 (q), 126.57, 127.76, 128.07, 128.84, 128.96, 129.20 (q), 129.45, 129.60, 133.02 (q), 136.23 (q), 138.49 (q), 143.68 (q), 147.09 (q), 163.10 (q); MS *m*/*z* 311 (M^+, 100), 310 (41), 309 (10). Anal. Calcd for $C_{21}H_{13}NS$: C, 81.00; H, 4.21; N, 4.50; S 10.29. Found: C, 81.15; H, 4.20; N, 4.55; S, 10.24.

Reaction of Isothiocyanate 6 with Tetrafluoroborate 1. Following method 1, column chromatography (light petroleum) gave unreacted 4-methoxyphenyl isothiocyanate (**6**). Further elution with light petroleum/diethyl ether 90:10 v/v afforded 9-methoxy-11-phenyl[1]benzothieno[2,3-*b*]quinoline (**11b**): mp 174−175 °C (from light petroleum/benzene).

Reaction of Isothiocyanate 7 with Tetrafluoroborate 1. Following methods 1 and 2, column chromatography (light petroleum) gave unreacted 4-methylphenyl isothiocyanate (**7**). Further elution with light petroleum/diethyl ether 80:20 v/v afforded an inseparable mixture of 9-methyl- (**11c**) and 8-methyl-11-phenyl[1]benzothieno[2,3-*b*]quinoline (**12c**) in ca. 5:1 ratio.

Reaction of Isothiocyanate 8 with Tetrafluoroborate 1. Following methods 1 and 2, column chromatography (light petroleum) gave unreacted 4-chlorophenyl isothiocyanate (**8**). Further elution with light petroleum/diethyl ether 90:10 v/v afforded an unresolved mixture of 9-chloro- (**11d**) and 8-chloro-11-phenyl[1]benzothieno[2,3-*b*]quinoline (**12d**). Subsequent flash chromatography using light petroleum/methylene chloride 60:40 v/v separated **11d**, mp 239−241 °C (from ethanol/benzene), and **12d**, mp 216−217 °C (from ethanol/benzene).

Reaction of Isothiocyanate 9 with Tetrafluoroborate 1. Following method 1, the resulting crude was shown by TLC to be especially complex. Attempted chromatographic separation gave unchanged 4-cyanophenyl isothiocyanate (**9**) and an unresolved mixture of unknown compounds. Following method 2, usual column chromatography (light petroleum/diethyl ether 90:10 v/v) gave, besides unchanged **9**, an unresolved mixture of 9-cyano- (**11e**) and 8-cyano-11-phenyl[1]benzothieno[2,3-*b*]quinoline (**12e**). Repeated chromatography of the isolated mixture on activated (basic) aluminum oxide, using light petroleum/methylene chloride 80:20 v/v as eluant, separated **11e**, mp 243−245 °C (from light petroleum/benzene), and **12e**, mp 230−231 °C (from light petroleum/benzene).

Reaction of Isothiocyanate 5 with Tetrafluoroborate 2. Following method 1, column chromatography (light petroleum/diethyl ether 90:10 v/v) gave unchanged **5**. Further elution with light petroleum/diethyl ether 80:20 v/v gave 2-cyano-11-phenyl[1]benzothieno[2,3-*b*]quinoline (**11f**), mp 235−237 °C (from light petroleum/benzene).

Reaction of Isothiocyanate 6 with Tetrafluoroborate 2. Following method 1, column chromatography (light petroleum/diethyl ether 90:10 v/v) gave unchanged **6**. Further elution with light petroleum/diethyl ether 80:20 v/v gave 2-cyano-9-methoxy-11-phenyl[1]benzothieno[2,3-*b*]quinoline (**11g**), mp 229−231 °C (from ethanol/benzene).

Reaction of Isothiocyanate 8 with Tetrafluoroborate 2. Following method 1, column chromatography (light petroleum) gave unchanged **8**. Further elution with light petroleum/diethyl ether 80:20 v/v gave 2-cyano-9-chloro-11-phenyl[1]-benzothieno[2,3-*b*]quinoline (**11h**), mp 253−255 °C (from ligroin/benzene), and 2-cyano-8-chloro-11-phenyl[1]benzothieno-[2,3-*b*]quinoline (**12h**), mp 209−211 °C (from ligroin/benzene).

Reaction of Isothiocyanate 9 with Tetrafluoroborate 2. Following method 1, column chromatography (light petroleum/diethyl ether 90:10) gave unchanged **9**. Further elution with light petroleum/methylene chloride 50:50 v/v gave a ca. 35:65 mixture of 2,9-dicyano-11-phenyl[1]benzothieno[2,3-*b*]-quinoline (**11i**) and the 2,8-dicyano isomer (**12i**). Repeated chromatography of this isomeric mixture, using light petroleum/methylene chloride/ethyl acetate 60:25:15 v/v as eluant, allowed separation of some pure compound **12i**, mp 331−333 °C (from benzene). Following method 2, analogous chromatographic work up led to the isolation of a strictly comparable mixture of the isomers **11i** and **12i**.

Semiempirical Calculations. Semiempirical calculations on radicals **14a**,**b**,**e**, **15a**,**b**,**e**, and **16a**,**b**,**e**, as well as the search for the reaction paths connecting **14**−**15** and **14**−**16** were carried out with the semiempirical program included in the

(18) Pazdera, P.; Ondracek, D. *Czech. Patent CS 270,981*, **1991** [*Chem. Abstr.* **1992**, *117*, 69590*u*].

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

Wavefunction PC Spartan Pro 1.0.3 package. After a careful conformational search, the geometries of the open-shell intermediates were fully optimized following the MNDO-d parametrization. A rough estimate of the transition-state geometry was then located by calculating the energy profile obtained by fixing the geometries of the open (vinyl **14**) and cyclized radical (cyclohexadienyls **15** or **16**) and varying in 10 steps the distance between the two atoms involved in the cyclization. The transition state geometry and energy were finally refined with the "transition-state-geometry" option of the semiempirical routine.

Energy values and differences for radicals **14a,b**,**e**, **15a**,**b**,**e**, and **16a**,**b**,**e** are reported in Table 3. The values showed, for all the calculated intermediates, a marked thermodynamic preference for six-membered cyclization, but with practically no influence of the Y-substituent. The charge densities for the radical center (d_1) and the *C*-N carbon (d_2) of radicals **14a**−**e** are reported in Table 4. The negative density on the vinylic carbon, and hence its nucleophilicity, is probably the result of a conjugative balance between the negatively charged nitrogen (ca. −0.2) and the positive sulfur (ca. 0.3), which produces a negative charge density on the aryl ring linked to the sulfur atom.

The activation barriers for cyclization of radicals **14a,b**,**e**, **15a**,**b**,**e,** and **16a**,**b**,**e** are reported in Table 3. All of the transition states are characterized by a single imaginary vibrational frequency (590.5, 592.4, and 597.2 cm^{-1} for the transition states leading to **15a**,**b**,**e** and 677.5, 673.6, and 685.8 cm^{-1} for those leading to **16a**,**b**,**e**) resulting from a negative force constant in the diagonal form of the Hessian; all of them collapse to the starting radicals when optimized without the "transition-state-geometry" option. The barrier differences (Table 3) are consistent with a marked kinetic preference for six-membered ring closure, but again with no significant dependence on the substitution pattern of the aryl ring involved in the cyclization. Actually, both substituents (OMe and CN) seem to diminish to some extent the thermodynamic and kinetic gap between the two competitive pathways, thus favoring intermediates **16** over radicals **15**, which is not in line with the experimental results.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, MS spectra, and elemental analyses for compounds **11b**−**i** and **12c**−**e**,**h,i** and geometries of radicals **14a**,**b**,**e**, **15a**,**b**,**e**, and **16a**,**b**,**e** and the corresponding transition states, as obtained by semiempirical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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