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Radical Annulations with Nitriles: Novel Cascade Reactions of Cyano-Substituted Alkyl and Sulfanyl Radicals with Isonitriles†

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Abstract: New radical annulation reactions are described involving addition of cyano-substituted alkyl and sulfanyl radicals to aromatic isonitriles. The tandem cyclisation of the resulting imidoyl radicals onto the cyano group affords cyclopenta- and thienoquinoxalines, respectively. The intervention of the isonitriles in the aromatisation process of the cyclohexadienyl radicals is discussed, as well as the regiochemistry of the cyclisation of the iminyl radicals obtained by addition of the imidoyls to the nitrile moiety. The hypothesis of an exclusive 6-membered ring closure onto the aromatic ring is also supported by the results of semiempirical AM1 calculations.

INTRODUCTION

The last decades have witnessed an explosive growth in the use of radical reactions and, in the future, there is likely to be a further spreading of free-radical-based methodologies in organic synthesis. Particularly, the radical addition, tandem cyclisation strategy has found appealing applications in cascade radical reactions that have allowed the construction of polycyclic molecules.[1] During the nineties, this procedure has been successfully employed in the synthesis of fused quinolines through generation and subsequent tandem cyclisation of suitable imidoyl radicals.[2] The antitumoral camptothecin and some analogues of that have been synthesised by this method.[2b-d]

Our interest in imidoyl radicals dates back to the mid eighties[3] and it prompted us to investigate other cascade reactions that could lead to potentially interesting heterocyclic compounds. In this regard we have recently reported the synthesis of quinoxaline derivatives through the first trimolecular version of the radical addition, tandem cyclisation strategy.[3i] This result encouraged the search for other annulations involving the facile 5-*exo*-*dig* cyclisation of the nucleophilic imidoyl radical onto a cyano group as a route to other heterocycles. Some results dealing with the addition of *ortho*-cyanophenyl radicals to arylisothiocyanates have just been published.[4] Here we report the reactions of some aromatic isonitriles with cyano-substituted alkyl and sulfanyl radicals affording substituted cyclopenta-, thieno-, and benzothienoquinoxalines.

RESULTS AND DISCUSSION

i. Alkyl Radicals. Iodide **1** (1 mmol), easily accessible from the commercially available bromo-derivative, was allowed to react at 150 °C with the isonitriles **2** (5 mmol) and hexamethylditin (1.5 mmol) in *tert*-butylbenzene (40 ml) solution under sunlamp irradiation.[2b] After 48 h, the reaction afforded the cyclopentaquinoxalines **3** and the amines **4** (Scheme 1, Table 1). Modifications in temperature or concentration resulted in lower yields of **3**.

† This paper is dedicated to Emeritus Professor Antonio Tundo on the occasion of his retirement.

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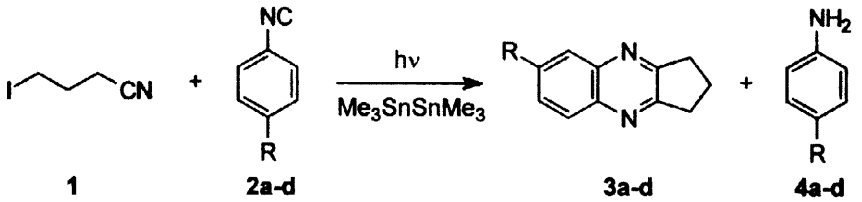


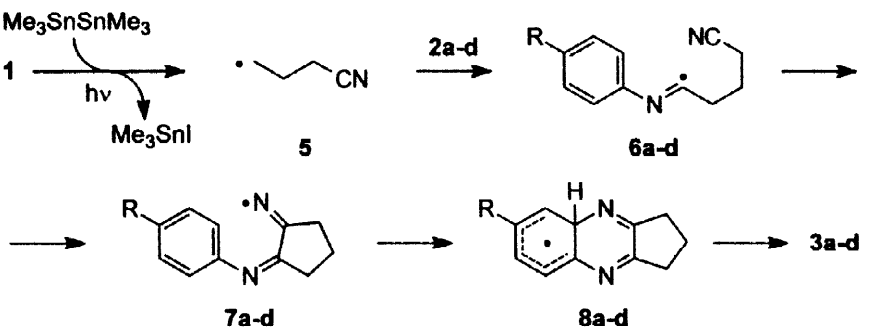
Scheme 1

Entry	R	3 (%)[a]
a	H	40
b	MeO	40
c	Cl	30
d	Ph	50

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

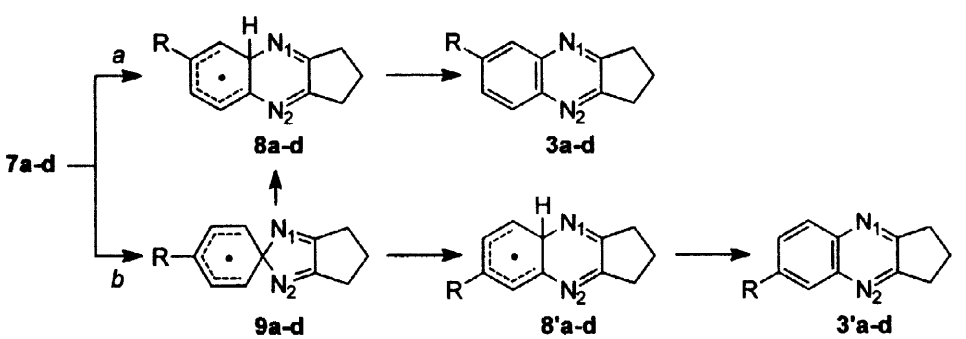
Table 1

The reaction mechanism can be described as shown in Scheme 2. Sunlamp irradiation of iodonitrile **1** brings about the homolyitc cleavage of the carbon-iodine bond with formation of iodine molecules that are scavenged by the distannane. Alternatively, the light-induced scission of the distannane generates tin radicals that abstract the iodine atom of **1**. Both routes give trimethyltin iodide and the alkyl radical **5**.[2b]



Scheme 2

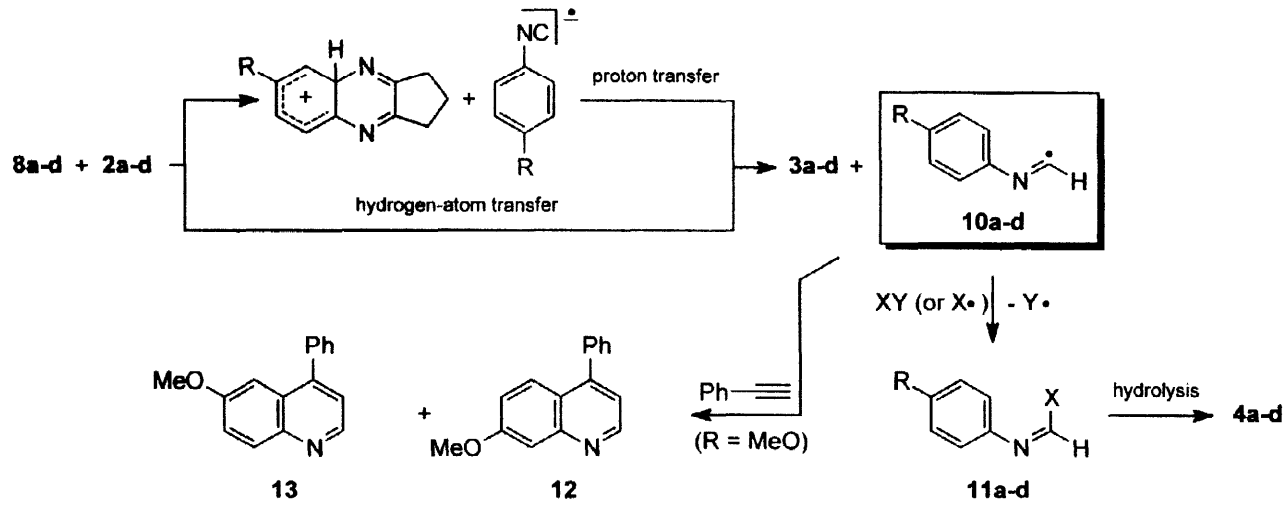
Addition of **5** to the isonitrile affords the imidoyl radical **6**; subsequent 5-*exo-dig* cyclisation of **6** onto the cyano group gives the iminyl **7**. Ring closure of **7** onto the aromatic ring eventually affords the cyclopentaquinoxaline **3** through aromatisation of the cyclohexadienyl radical **8**. The feasibility of the above steps has been already discussed.[3i,4] The possibility that iminyl **7** could give rise to both 6- and 5-membered ring closure, similarly to what has been reported for analogous iminyl radicals in the gas phase,[5] should be taken into account (Scheme 3, paths *a* and *b*).



Scheme 3

Nevertheless, in the case of the intermediate **7**, this behaviour would result in the formation of identical products (**3a-d** and **3'a-d**). Therefore, its likelihood will be discussed in the section dealing with the addition of sulfanyl radicals (see below).

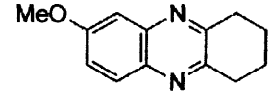
The formation of amines **4** — in up to 10% yield — was unexpected, since they cannot derive from any reasonable side-reaction of the isonitriles.[6] In the light of previous results, which suggested the intervention of isonitriles in the aromatisation of cyclohexadienyl radicals,[3i] the amines **4** can be accounted for through the mechanism depicted in Scheme 4.



Scheme 4

Electron-transfer between the cyclohexadienyl radical **8** and the isonitrile followed by proton transfer — or, alternatively, direct hydrogen-atom transfer between the two species — generates the aromatic compound **3** and the α-unsubstituted imidoyl radical **10**. Trapping of **10** by a radical species or a radical displacement reaction would afford the imine **11**, whose hydrolysis could most likely lead to the amines **4**.[7] The intermediacy of imidoyl radical **10** was proved by carrying out the reaction **b** (R = MeO) in the presence of phenylacetylene. With this alkyne, imidoyl radicals are known to give both [4 + 2] and [3 + 2] radical annulations yielding mixtures of isomeric quinolines.[3c,i,j] In particular, **10b** has been reported to afford a 3:1 mixture of the isomeric products **12** and **13**.[3i] When the iodide **1** was allowed to react with isonitrile **2b** under the usual conditions in the presence of phenylacetylene, it gave small amounts of a nearly 3:1 mixture of **12** and **13**. This is undoubtedly a supporting evidence of the intermediacy of radical **10** and thence of the intervention to some extent of the isonitrile-mediated aromatisation of the cyclohexadienyl radicals.

Attempts to synthesise cyclohexa-fused quinoxalines by an analogous methodology were unsatisfactory. The reaction of 5-iodovaleronitrile with isonitrile **2b** in the presence of hexamethylditin and sunlamp irradiation gave, under various conditions, quinoxaline **14** in yields ranging from trace amounts to only 10%. It is reasonable to suppose that this reaction could be strongly affected by a 1,5-hydrogen shift from the methylene linked to the cyano group. This kind of process, which is likely to be very fast,[8] would trap the imidoyl radical preventing cyclisation onto the nitrile moiety.



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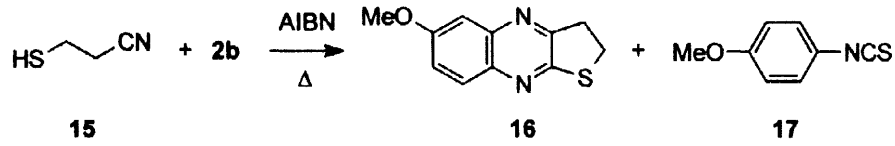
ii. Sulfanyl Radicals. The addition of cyano-substituted sulfanyl radicals to isonitriles was first studied with aliphatic sulfanyls suitable for 5-*exo-dig* cyclisations of the resulting imidoyl radicals onto the carbon-nitrogen triple bond. They were generated by hydrogen-atom abstraction from the corresponding thiols or photolytic cleavage of appropriate disulfides. It is worth pointing out that the addition of sulfanyl radicals to isonitriles has been known since 1970,[9] but the applications of this reaction in organic synthesis are still somewhat rare.[9d,e]

The thiol **15** (1 mmol), easily prepared from the commercially available 3-bromopropionitrile, was allowed to react with isonitrile **2b** (2 mmol) and azo-bis-*iso*-butyronitrile (AIBN) in boiling toluene (40 ml).

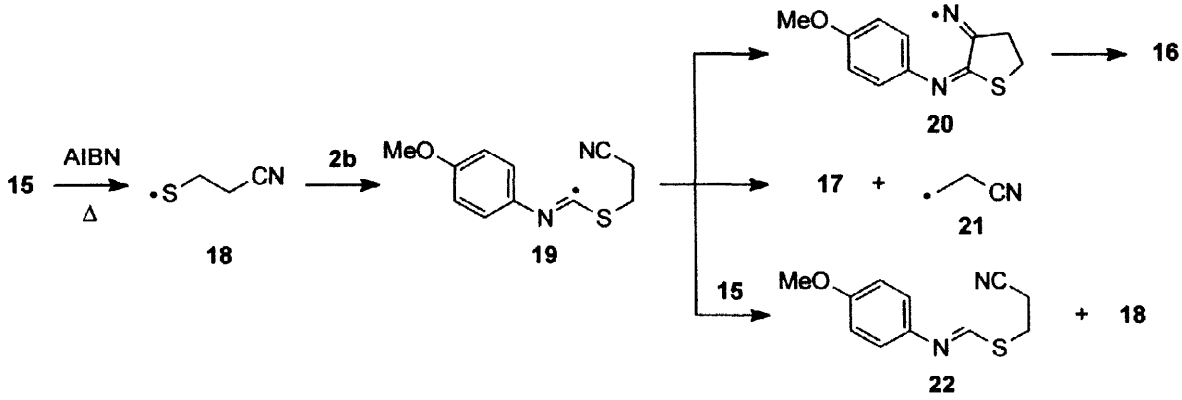
After 1.5 h, the reaction afforded the unreported thienoquinoxaline **16** and the isothiocyanate **17** in 14% and 60% yield, respectively (Scheme 5). Trace amounts of *p*-anisidine **4b** were detected as well.



15 **16** **17**

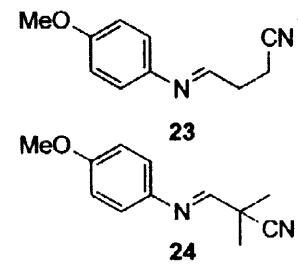
Scheme 5

The reaction mechanism is reported in Scheme 6. Decomposition of AIBN produces 2-cyano-*iso*-propyl radicals that abstract the hydrogen atom from **15** giving sulfanyl **18**. Analogously to what claimed for radical **5**, **18** can add to the carbon atom of **2b** giving the imidoyl **19**. Tandem cyclisations of **19** onto the cyano group and the resulting iminyl **20** onto the aromatic ring lead to the thienoquinoxaline **16**. Imidoyl **19** can also give a competitive β-fragmentation with formation of isothiocyanate **17** and release of a 2-cyanoethyl radical **21**.



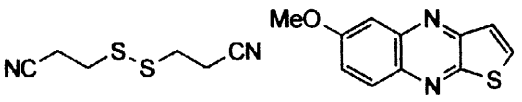
Scheme 6

The formation of **21** was supported by a GC-MS analysis of the reaction mixture, which showed the presence of small amounts of compound **23**, resulting from addition of **21** to **2b** and subsequent hydrogen abstraction. By GC-MS analysis of the reaction crude we also detected small quantities of compounds **22** and **24**, the former arising from reduction of **19** and the latter from addition of 2-cyano-*iso*-propyl radicals to **2b** followed by hydrogen abstraction. As one can see, the addition of sulfanyl radicals to isonitriles seems to be a very efficient process (the overall yield of compounds deriving from radical **19** is nearly 75%). Unfortunately, the annulation efficiency is strongly reduced by the competitive β-scission of radical **19**, which is highly favoured under these conditions. Actually, the formation of isothiocyanates from α-(*tert*-alkylthio)imidoyl radicals has been reported,[9a] but we were quite astonished at finding that radical **19** prefers so strongly this route even when a primary alkyl radical is formed.



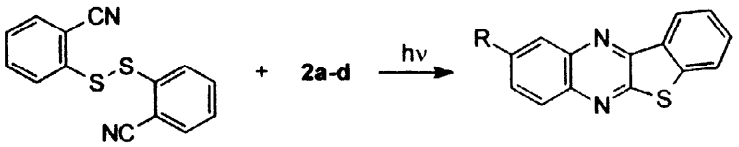
To prevent fragmentation, we carried out the reaction at lower temperatures with sunlamp-initiated decomposition of AIBN. At room temperature, compounds **16** and **17** were formed in 20% and 15% yield, respectively, and a GC-MS analysis showed a considerable increase in the amount of **22**. At -78 °C, the quinoxaline **16** was not formed at all and, besides trace amounts of **17**, the reaction yielded the thioformimidate **22** in almost quantitative yield.[10] At this temperature, the β-fragmentation is nearly suppressed but, at the same time, the 5-*exo* ring closure is so slow that the imidoyl radical **19** is completely trapped by the thiol prior to cyclisation. Therefore, we tried to overcome this problem by carrying out the reaction with a different source of sulfanyl radicals, *i.e.*, the disulfide **25**. UV photolysis of **25** at r.t. in the presence of **2b** gave, after 48 h, a 3:1 mixture of **16** and **17** and small amounts of the thiol **15**. Unfortunately, even after many days, we were not able to obtain more than 50% conversion of the starting disulfide, probably

due to radiation quenching by some tarry materials. The reaction afforded quinoxaline **16** in an acceptable 35% yield, based on the reacted disulfide. It is worth noting that **16** was never contaminated, neither under these conditions nor in the presence of AIBN, by any trace of the fully aromatic compound **26**, easily prepared by DDQ oxidation of **16**.



25 **26**

Finally, we turned our attention to aromatic disulfides. We reasoned that, due to the lower sulfur-sulfur bond energy, an aromatic disulfide should be a better photolytic source of sulfanyl radicals. In addition, the strong sulfur-carbon bond should discourage the β-fragmentation to isothiocyanate, and, again, the absence of mobile hydrogen atoms is expected to prevent reduction of the imidoyl radical. Our expectations were actually fulfilled by the reaction of disulfide **27** with isonitriles **2a-d** under UV photochemical initiation. Under these conditions, the benzothienoquinoxalines **28a-d** were formed in fair yields (Scheme 7, Table 2).



27 **2a-d** **28a-d**

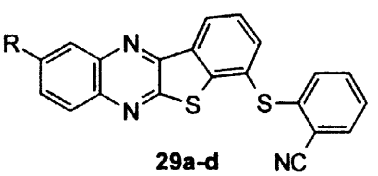
Scheme 7

Entry	R	**28** (%)[a]
a	H	40
b	MeO	55
c	Cl	70
d	Ph	65

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

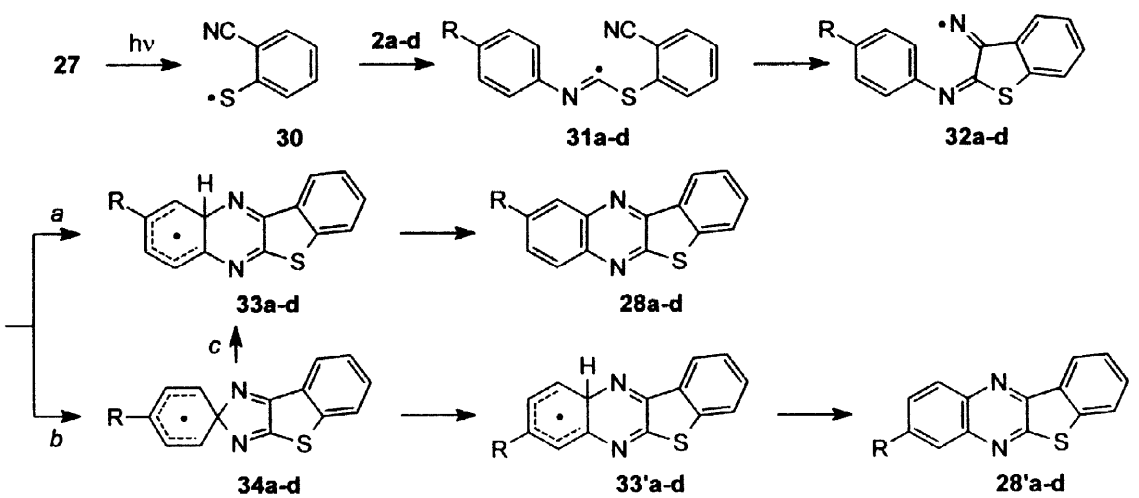
Table 2

This procedure gave much cleaner reaction mixtures and the starting disulfide **27** was completely converted in 3-24 h. The only identifiable by-products were the benzothienoquinoxalines **29a-d**. They were formed in small amounts and can reasonably derive from addition of another sulfanyl radical to **28a-d**.[11]



29a-d

The iminyl radicals **32a-d**, obtained by cyclisation of imidoyls **31a-d**, could actually lead to different isomeric derivatives (**28a-d** and **28'a-d**) if a competitive 5-membered ring closure would occur (Scheme 8).



30 **31a-d** **32a-d** **33a-d** **28a-d** **34a-d** **33'a-d** **28'a-d**

Scheme 8

The reaction certainly afforded only one product, but it could be argued that we cannot actually distinguish between structures **28** and **28'**.[12] A complete discussion about the three possible annulation routes (Scheme 8, paths *a*, *b*, and *c*) and the actual structure of the reaction product has been reported in a recent paper.[4] In that study, imidoyl radicals **31** have been generated by addition of 2-cyanophenyl radicals to arylisothiocyanates and the final product has been claimed to have structure **28**. Here, we would like to emphasise that isolation of compound **29** — whose structure was unambiguously determined — is the final evidence of the reaction outcome. As a matter of fact, there is no plausible reason for believing that the spirocyclohexadienyl radical **34** would rearrange by migration of one carbon-nitrogen bond only (path *c*). If **34** were formed, it should rather afford both cyclohexadienyl radicals **33** and **33'**. Therefore, we can reasonably state that iminyl **32** gives a direct 6-membered cyclisation to **33** and then to the benzothienoquinoxaline **28** (path *a*). Path *b* does not seem to occur to a significant extent.

Semiempirical calculations according to the AM1 method fully support the formation of the six-membered cyclisation product **33** as the main reaction pathway. Both relative stability of the cyclohexadienyl radicals **33** and **34** and the transition states leading to the cyclisation products (Figure 1) indicate that the spiro-cyclisation is energetically unfavoured. A classical rationalisation of the quanto-mechanichal result is the loss of delocalisation following the cyclisation pathway *b*: the unpaired electron in **33** is delocalised on the whole π-system of the molecule; this is not possible in radical **34**, because of the tetrahedral structure of the spiro-carbon atom. On the other hand, the relatively small activation barrier for the opening of the spiro intermediate **34** suggests that - when formed - a spirocyclohexadienyl radical could actually revert to an open radical, giving the isomerisation reactions described elsewhere.

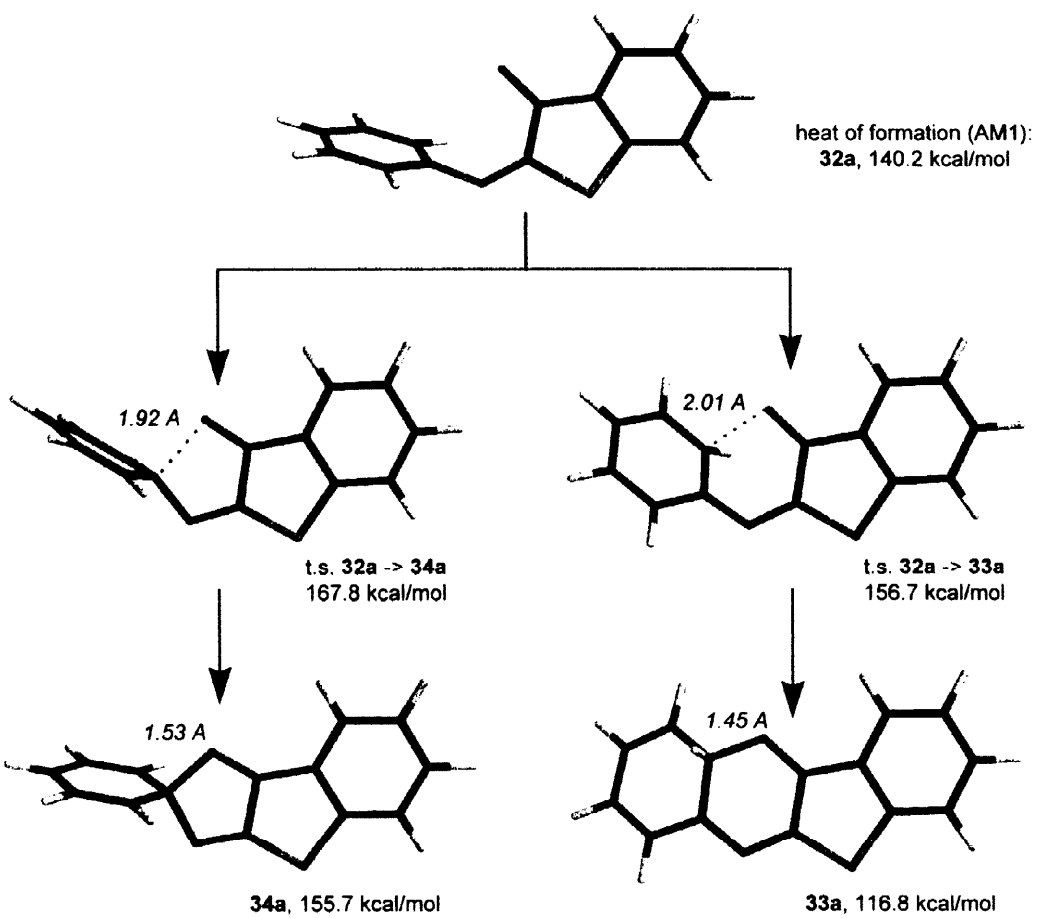


Figure 1

CONCLUSIONS

The results reported in this paper show once more that radical addition to isonitriles is an appealing process that can lead to a variety of heterocyclic molecules through cascade radical reactions. With alkyl radicals **5** cyclopentaquinoxalines are formed together with minor amounts of amines. The latter compounds presumably arise from hydrolysis of imine derivatives that are the result of the intervention of the starting isonitriles in the aromatisation of cyclohexadienyl radicals. The formation of quinoxalines with larger fused rings appears to be hindered by side reactions, probably intramolecular hydrogen-abstraction processes. If this is the case, the problem could be circumvented by replacing a methylene with other non-radicophilic moieties: studies on this subject are underway. The addition of sulfanyl radicals seems in general more efficient but, when the sulfanyl is generated from alkyl thiols, is limited in scope by the ease of β-fragmentation and hydrogen-abstraction reactions of the resulting α-thioimidoyl radicals. Indeed, the reactions of radicals **18** with isonitriles afforded thienoquinoxalines, isothiocyanates, and thioformimidates. When the sulfanyl radicals are generated by UV-initiated homolysis of disulfides the reactions are more selective and, in the case of aromatic sulfanyls, give benzothienoquinoxalines in fair yields. In principle, the final iminyl radicals could give rise to both five- and six-membered cyclisations onto the aromatic isonitrile ring, leading to the different quinoxaline derivatives **28** and **28'**. Nevertheless, only one benzothienoquinoxaline isomer is always formed and this is explained in terms of a direct 6-membered ring closure of the iminyl. This belief is also supported by semiempirical AM1 calculations. In our opinion, this methodology could be successfully extended to other unsaturated isonitriles and/or carbon- or heteroatom-centred radicals bearing radicophilic groups in the side chain. Therefore, studies are in progress to apply these cascade radical reactions to the synthesis of a series of heterocycles as wide as possible.

EXPERIMENTAL SECTION

General Procedures.

Melting points were determined on an Electrothermal capillary apparatus and are uncorrected. ^{1}H-NMR spectra were recorded in deuterochloroform on Varian Gemini 200 (200 MHz) or Gemini 300 (300 MHz) instruments, using tetramethylsilane as an internal standard. Mass spectra (MS) and high resolution mass spectra (HRMS) were performed with a VG 7070E spectrometer by electron impact with a beam energy of 70 eV. IR spectra were recorded in chloroform on a Perkin-Elmer 257 spectrophotometer. GC-MS analyses were carried out on a Carlo Erba AUTO/HRGC/MS-QMD 1000 instrument equipped with a Quadrex capillary column (007, 25 m x 0.25 mm I.D.) and a NIST/NBS library. Photolysis of iodides and AIBN was carried out with an Osram Ultra-Vitalux sunlamp (300 W); UV photolysis of disulfides was performed with a Heraeus TQ 150 high-pressure mercury lamp (150 W). Column chromatography was carried out on silica gel (ICN Silica, 63-200, 60 A) using light petroleum (40-70 °C) and a light petroleum/diethyl ether gradient (from 0 up to 100% diethyl ether) as eluant. Previously reported reaction products were identified by spectral comparison and mixed mp determination with authentic specimens.

Starting Materials.

3-Bromopropionitrile, 4-bromobutyronitrile, 5-bromovaleronitrile, aniline, 4-methoxyaniline, 4-chloroaniline, 4-aminobiphenyl, diphosgene, hexamethylditin, DDQ, phenylacetylene, azo-bis-*iso*-butyronitrile (AIBN), 4-methoxyphenylisothiocyanate (**17**), and *tert*-butylbenzene were commercially available (Aldrich). AIBN was purified by being dissolved in chloroform and reprecipitated with methanol. 4-Iodobutyronitrile (**1**, bp [15 mmHg] = 109-111 °C)[13] and 5-iodovaleronitrile (bp [1 mmHg] = 98 °C)[14] were prepared by treatment of the corresponding bromides with sodium iodide in acetone.[13] Phenylisonitrile (**2a**, bp [11 mmHg] = 50-51 °C),[15] 4-methoxyphenylisonitrile (**2b**, bp [1 mmHg] = 76-78 °C),[16] and 4-chlorophenylisonitrile (**2c**, mp = 71 °C)[17] were prepared according to the literature[15] by reaction of the corresponding formamides with diphosgene and triethylamine. 3-Mercaptopropionitrile (**15**),[18]

3,3'-dithio-bis-propionitrile (**25**),[19] 2,2'-dithio-bis-benzonitrile (**27**),[20] 6-methoxy-4-phenylquinoline (**13**),[21] and 7-methoxy-4-phenylquinoline (**12**)[22] were prepared according to the literature.

4-Isocyanobiphenyl (2d). According to the procedure reported for other isonitriles,[15] a solution of diphosgene (0.16 mol) in anhydrous dichloromethane (65 mL) was added dropwise at 0 °C in 1 h to a stirred solution of 4-formamidobiphenyl[23] (19.7 g, 0.1 mol) and anhydrous triethylamine (0.69 mol) in dichloromethane (150 mL). The reaction vessel must be equipped with a condenser kept at -30 °C. The mixture was stirred for additional 30 min at 0 °C and then warmed to 25 °C. Water (100 mL) was added and the organic phase was separated, washed with an aqueous sodium bicarbonate solution (7.5 %), and dried over calcium chloride. The solvent was evaporated and the residue chromatographed on silica gel eluting with light petroleum / ethyl acetate (97:3 v/v) to give the title compound (13.4 g, 75%), mp = 77-79 °C; 200 MHz ^{1}H-NMR δ 7.27-7.53 (9 H, m); ν_{max} 3000, 2130, 1660, 1490 cm^{-1}; MS *m/e* (rel inten) 179 (M^+, 100), 178 (66), 177 (27), 153 (13), 152 (21), 151 (36), 76 (30), 63 (19), 51 (17). Anal. calcd for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.82. Found: C, 87.08; H, 5.07; N, 7.85.

Reactions of iodide 1 with isonitriles.

General procedure. A degassed solution of iodonitrile **1** (1 mmol), isonitrile **2** (5 mmol), and hexamethylditin (1.5 mmol) in *tert*-butylbenzene (40 mL) was kept at 150 °C for 48 h under sunlamp irradiation (sealed Pyrex tube kept for one-third in a silicon-oil bath and at 5 cm from the lamp). Disappearance of the starting iodide was monitored by GC-MS. After removal of the solvent, the residue was chromatographed to give quinoxalines **3** and amines **4** (**4a**, 5%; **4b**, 10%; **4c**, trace amounts; **4d**, 5%). The following quinoxalines were obtained according to this general procedure in the yields reported in Table 1.

Cyclopenta[1,2-b]quinoxaline (3a), mp = 99-101 °C (lit.[24] mp = 100-101 °C).

6-Methoxycyclopenta[1,2-b]quinoxaline (3b), mp = 86-87 °C (from light petroleum); 300 MHz ^{1}H-NMR δ 2.29 (2 H, quintet, J = 7.5 Hz, 2-CH_2), 3.13-3.20 (4 H, 2 overlapped triplets, $J_1 = J_2$ = 7.5 Hz, 1-CH_2 + 3-CH_2), 3.92 (3 H, s, OMe), 7.28-7.33 (2 H, m, Ar-H), 7.87 (1 H, m, Ar-H); MS *m/e* (rel inten) 200 (M^+, 100), 199 (38), 185 (66), 169 (18), 157 (55), 156 (22). Anal. calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.10; H, 6.06; N, 13.95.

6-Chlorocyclopenta[1,2-b]quinoxaline (3c), oil; 200 MHz ^{1}H-NMR δ 2.28 (2 H, quintet, J = 7.0 Hz, 2-CH_2), 3.16-3.18 (4 H, 2 overlapped triplets, $J_1 = J_2$ = 7.0 Hz, 1-CH_2 + 3-CH_2), 7.58 (1 H, dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, Ar-H), 7.90 (1 H, d, J = 8.3 Hz, Ar-H), 7.96 (1 H, d, J = 1.8 Hz, Ar-H); MS *m/e* (rel inten) 206 (M^+ + 2, 23), 205 (M^+ + 1, 27), 204 (M^+, 86), 203 (100), 176 (11), 168 (20). Anal. calcd for $C_{11}H_9ClN_2$: C, 64.56; H, 4.43; N, 13.69. Found: C, 64.63; H, 4.42; N, 13.66.

6-Phenylcyclopenta[1,2-b]quinoxaline (3d), oil; 200 MHz ^{1}H-NMR δ 2.18 (2 H, quintet, J = 7.2 Hz, 2-CH_2), 3.09 (4 H, t, J = 7.2 Hz, 1-CH_2 + 3-CH_2), 7.20-7.60 (5 H, m, Ar-H), 7.84 (1 H, dd, J_1 = 8.7 Hz, J_2 = 1.9 Hz, Ar-H), 7.98 (1 H, d, J = 8.7 Hz, Ar-H), 8.14 (1 H, d, J = 1.9 Hz, Ar-H); MS *m/e* (rel inten) 246 (M^+, 100), 245 (91), 218 (4), 151 (10), 123 (16). Anal. calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.97; H, 5.71; N, 11.32.

Reaction of 5-iodovaleronitrile with 2b. According to the general procedure, the reaction yielded *7-methoxycyclohexa[1,2-b]quinoxaline* (**14**, 10%), oil [200 MHz ^{1}H-NMR δ 2.03 (4 H, m, 2-CH_2 + 3-CH_2), 3.12 (4 H, m, 1-CH_2 + 4-CH_2), 3.94 (3 H, s, OMe), 7.26-7.36 (2 H, m, Ar-H), 7.85 (1 H, d, J = 8.7 Hz, Ar-H); MS *m/e* (rel inten) 214 (M^+, 100), 213 (15), 199 (42), 186 (6), 171 (20). Anal. calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.94; H, 6.57; N, 13.04] and 4-methoxyaniline (**4b**, 33%).

Reaction of 1 with 2b in the presence of phenylacetylene (1 mmol). According to the general procedure, the reaction yielded **3b** (35%), **4b** (2%), and a 3:1 mixture of quinolines **13**[21] and **12**[22] (0.02 g), identified by spectral comparison with a mixture of authentic specimens. The isomer ratio was determined by integration of the ^{1}H NMR signals of the two methoxy groups.

Reactions of thiol 15 with isonitrile 2b.

Reaction in boiling toluene. A toluene (40 mL) solution of **15** (1 mmol), **2b** (2 mmol), and AIBN (0.15 mmol) was refluxed for 1.5 h. After removal of the solvent, the residue was chromatographed to give *2,3-dihydro-6-methoxythieno[2,3-b]quinoxaline* (**16**) (0.03 g, 14%), mp = 125-127 °C [200 MHz ^{1}H-NMR δ 3.50 (4 H, s, 2-CH_2 + 3-CH_2), 3.90 (3 H, s, OMe), 7.22-7.31 (2 H, m, Ar-H), 7.76 (1 H, m, Ar-H); MS *m/e* (rel inten) 218 (M^+, 100), 216 (16), 203 (61), 175 (28). Anal. calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.59; H, 4.61; N, 12.79; S, 14.73], *4-methoxyphenylisothiocyanate* (**17**) (0.1 g, 60%), and **4b** (trace amounts).

Reaction in toluene at r.t.. A toluene (40 mL) solution of **15** (1 mmol), **2b** (2 mmol), and AIBN (0.5 mmol) was kept at r.t. for 4 h under a nitrogen atmosphere and sunlamp irradiation. After removal of the solvent, the residue was chromatographed to give **16** (0.045 g, 20%), **17** (0.025 g, 15%), and **4b** (traces).

By GC-MS analysis, both reactions also afforded small, variable amounts of *N-(3-cyanopropylidene)-4-methoxyaniline* (**23**) [MS *m/e* (rel inten) 188 (M^+, 52), 173 (35), 146 (10), 134 (100), 107 (25), 92 (25), 77 (40)] and *N-(2-cyano-2-methylpropylidene)-4-methoxyaniline* (**24**) [MS *m/e* (rel inten) 202 (M^+, 10), 134 (100), 107 (19), 92 (14), 77 (23)].

Reaction in toluene at -78 °C. A toluene (40 mL) solution of **15** (1 mmol), **2b** (2 mmol), and AIBN (0.5 mmol) was kept at -78 °C for 5 h under a nitrogen atmosphere and sunlamp irradiation. GC-MS and ^{1}H-NMR analyses of the reaction crude showed the absence of **16** and the presence of **4b** (trace amounts) and *2-cyanoethyl N-(4-methoxyphenyl)thioformimidate* (**22**) as the almost exclusive product [200 MHz ^{1}H-NMR (reaction crude) δ 2.84 (2 H, t, J = 7.0 Hz, -CH_2-), 3.30 (2 H, t, J = 7.0 Hz, -CH_2-), 3.78 (3 H, s, OMe), 6.82 (2 H, A part of AA'BB', J = 9.0 Hz, Ar-H), 7.00 (2 H, B part of AA'BB', J = 9.0 Hz, Ar-H), 8.37 (1 H, s, N=CH); MS *m/e* (rel inten) 220 (M^+, 18), 167 (22), 134 (100), 107 (32), 92 (25), 77 (43); HRMS calcd for $C_{11}H_{12}N_2OS$ 220.0670, found 220.0672].

Reaction of disulfide 25 with isonitrile 2b. A benzene (40 mL) solution of **25** (0.5 mmol) and **2b** (5 mmol) in a quartz Erlenmeyer flask was kept at r.t. for 48 h under a nitrogen atmosphere and UV irradiation. After removal of the solvent, the residue was chromatographed to give **16** (0.03 g, 14%, 35% based on the reacted disulfide), a mixture of **17** and **2b** (0.01 g), thiol **15** (trace amounts), and starting **25** (0.10 g).

Aromatisation of 16. A benzene (55 mL) solution of **16** (0.04 g, 0.18 mmol) and DDQ (0.04 g, 0.18 mmol) was refluxed for 5 min. The solvent was evaporated and the residue chromatographed to give 0.02 g (51%) of *6-methoxythieno[2,3-b]quinoxaline* (**26**), mp = 134-136 °C; 300 MHz ^{1}H-NMR δ 4.00 (3 H, s, OMe), 7.43-7.49 (2 H, m, Ar-H), 7.53 (1 H, d, J = 6.3 Hz, Ar-H), 8.01-8.07 (2 H, d + m, J = 6.3 Hz, Ar-H); MS *m/e* (rel inten) 216 (M^+, 100), 201 (16), 186 (16), 173 (60). Anal. calcd for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.95; S, 14.83. Found: C, 61.15; H, 3.72; N, 12.91; S, 14.87.

Reactions of disulfide 27 with isonitriles.

General procedure. A benzene (40 mL) solution of **27** (0.5 mmol) and **2** (5 mmol) in a quartz Erlenmeyer flask was kept at r.t. for 3-24 h under a nitrogen atmosphere and UV irradiation. After removal of the solvent, the residue was chromatographed to give quinoxalines **28** in the yields reported in Table 2. The following quinoxalines were obtained according to this general procedure.

Benzo[4,5]thieno[2,3-b]quinoxaline (28a), mp = 165-167 °C (from ethanol) (lit.[25] mp = 166-167 °C).

9-Methoxybenzo[4,5]thieno[2,3-b]quinoxaline (28b), mp = 185-187 °C (from ethanol/chloroform) (lit.[4] mp = 187-188 °C).

9-Chlorobenzo[4,5]thieno[2,3-b]quinoxaline (28c), mp = 224-226 °C (from benzene) (lit.[4] mp = 224-226 °C).

9-Phenylbenzo[4,5]thieno[2,3-b]quinoxaline (28d), mp = 198-201 °C (from benzene); 200 MHz ^{1}H-NMR δ 7.34-7.56 (4 H, m + ddd, $J_1 = J_2 = 7.3$ Hz, $J_3 = 1.3$ Hz), 7.61 (1 H, ddd, $J_1 = J_2 = 7.3$ Hz, $J_3 = 1.5$ Hz), 7.70-7.85 (3 H, m), 8.03 (1 H, dd, $J_1 = 8.8$ Hz, $J_2 = 1.9$ Hz), 8.16 (1 H, d, $J = 8.8$ Hz), 8.43 (1 H, d, $J_1 = 1.9$ Hz), 8.53 (1 H, m); MS *m/e* (rel inten) 312 (M^+, 100), 311 (13), 156 (15). Anal. calcd for $C_{20}H_{12}N_2S$: C, 76.90; H, 3.87; N, 8.97; S, 10.26. Found: C, 76.98; H, 3.86; N, 8.94; S, 10.22.

Reactions **b**, **c**, and **d** also afforded small amounts of compounds which, on the basis of the X-ray crystallography of the methoxy derivative (reaction **b**), were tentatively given structures **29b-d**. Whereas compound **29b** was unambiguously characterised, the structures of the other analogues need some more investigation, particularly on the exact position of the (cyanophenyl)thio-group.[11] Here we report preliminar spectral data of these products.

29b (7%): 200 MHz ^{1}H-NMR δ 4.03 (3 H, s, OMe), 7.08-7.16 (1 H, m), 7.28 (1 H, ddd, $J_1 = J_2 = 7.6$ Hz, $J_3 = 1.5$ Hz), 7.38 (1 H, ddd, $J_1 = J_2 = 7.6$ Hz, $J_3 = 1.7$ Hz), 7.49 (1 H, dd, $J_1 = 9.1$ Hz, $J_2 = 2.7$ Hz), 7.54 (1 H, d, $J = 2.7$ Hz), 7.61-7.72 (2 H, t + m, $J = 7.6$ Hz), 7.92 (1 H, dd, $J_1 = 7.6$ Hz, $J_2 = 1.0$ Hz), 8.04 (1 H, d, $J_1 = 9.1$ Hz), 8.62 (1 H, dd, $J_1 = 7.6$ Hz, $J_2 = 1.0$ Hz); ν_{max} 3000, 2230, 1625, 1605, 1330, 1100 cm^{-1}; MS *m/e* (rel inten) 400 ($M^+ + 1$, 100), 385 (6), 357 (17), 200 (6).

29c (10%): MS *m/e* (rel inten) 405 ($M^+ + 2$, 44), 404 ($M^+ + 1$, 29), 403 (M^+, 100), 402 (10), 301 (7), 202 (8), 133 (8); HRMS calcd for $C_{21}H_{10}ClN_3S_2$ 403.0005, found 403.0008.

29d (5%): 200 MHz ^{1}H-NMR δ 7.17 (1 H, m), 7.26-8.00 (10 H, m), 8.10-8.29 (2 H, m), 8.48-8.54 (1 H, m), 8.65-8.76 (1 H, m); MS *m/e* (rel inten) 445 (M^+, 100), 444 (6), 343 (5), 223 (11); HRMS calcd for $C_{27}H_{15}N_3S_2$ 445.0707, found 445.0700.

Semiempirical calculations. Semiempirical calculations on radicals **32**, **33** and **34**, as well as the search for the reaction path connecting **32** - **33** and **32** - **34** were carried out with the *Spartan plus* package running on a Power Macintosh computer. The geometries of the open-shell intermediates were fully optimised following the AM1 parametrisation. A rough extimate of the transition-state geometry was then located by fixing the distance between the attaching iminyl nitrogen and the *ipso* - or *ortho* position in 0.1 - 0.01 A steps. At each step all the remaining degrees of freedom were fully minimised. Transition state geometry (and energy) was then refined following the "saddle" algorithm as programmed in the *Spartan plus* package. The transition states were characterised by a single imaginary vibrational frequency (637.3 cm^{-1} and 763.6 cm^{-1} for the transition states leading to **33** and **34** respectively) resulting from a negative force constant in the diagonal form of the Hessian, and collapse to the starting products when the "saddle" option is removed.

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6. Hydrolysis of the isonitriles — in the reaction mixture or during column chromatography — should afford the corresponding formamides, which showed no tendency to hydrolyse further to amines under the reaction conditions or chromatographic work up. The only other by-products expected were the corresponding nitriles, since isonitriles are known to isomerise under various conditions (see: Casanova, J.; Werner, N. D.; Schuster, R. E. *J. Org. Chem.* **1966**, *31*, 3473. Wolber, E. K. A.; Schmittel, M.; Rüchardt, C. *Chem. Ber.* **1992**, *125*, 525). Actually, considerable amounts of nitriles were formed during the reactions. Of course, all of the reactions were carried out with isonitriles uncontaminated by any significant trace of amines.
7. Compound **11** could also be trapped by the excess isonitrile to give polymeric products and tars, which were actually detected in the reaction mixtures. Evidence for the formation of **11** was not obtained, neither by NMR spectroscopy nor by GC-MS analysis of the reaction crude. On the other hand, these compounds are expected to be very easily hydrolysed, especially if R is a trimethyltin moiety.
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10. Determined by ^{1}H-NMR analysis of the reaction crude (see Experimental Section).
11. Compound **29b** was unambiguously identified by X-ray crystallography. The structure of this compound and the homogeneity of the sample — confirmed by ^{1}H-NMR analysis — seem to indicate an unexpected, selective addition of the sulfanyl radical to the 4-position of **28b**. In our opinion, this outcome is worthy of further investigation: the results will be published elsewhere, together with the X-ray structure of **29b**.
12. We never succeeded in obtaining crystals of the reaction products suitable for X-ray crystallographic determinations.

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