Radical Addition to Isonitriles: A Route to Polyfunctionalized Alkenes through a Novel Three-Component Radical Cascade Reaction

Rino Leardini, Daniele Nanni,* and Giuseppe Zanardi
Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, Viale Risorgimento 4, I-40136 Bologna, Italy

Received December 6, 1999

The reaction of aromatic disulfides, alkenes, and isonitriles under photolytic conditions affords polyfunctionalized alkenes—β-aryltiio-substituted acrylamides or acrylonitriles—in fair yields through a novel three-component radical cascade reaction. The procedure entails addition of a sulfanyl radical to the alkyne followed by attack of the resulting vinyl radical to the isonitrile. A fast reaction, e.g., scavenging by a nitro derivative or β-fragmentation, is necessary in order to trap the final imidoyl radical, since addition of vinyl radicals to isonitriles seems to be a reversible process. The stereochemistry of the reaction is discussed, particularly with respect to the stereochemical outcome of related hydro-Gen abstractions by the same vinyl radicals. The lower or even inverted preference for either geometrical isomer observed in our cases with respect to that encountered in hydro-Gen abstraction reactions is explained in terms of transition-state interactions and/or isomerization of the final imidoyl radical. The latter possibility is supported by semiempirical calculations, which show that the spin distribution in the imidoyl radical can allow rotation of the adjacent carbon–carbon double bond prior to β-fragmentation.

Introduction

Radical addition to isonitriles dates back to the 1960s, when Shaw and Saegusa discovered the isonitrile–nitrile isomerization mediated by methyl1a or stannyl radicals.1b Until recent years, this reaction has been studied both from a mechanistic and a synthetic point of view,2 especially as an approach to nitriles2i or a deamination method.2j

Only since 1991 have radical reactions with isonitriles been successfully employed in the synthesis of heterocyclic compounds.3 In his pioneering work,3a Curran carried out several 4 + 1 annihilations using isonitriles as geminal radical acceptor/radical donor synthons: this strategy allowed the synthesis of cyclopenta-fused quinolines and provided easy access to the antitumor agents of the camptothecin family.3b,e,h,i,l,n Almost in the same years, Bachi performed studies on the free-radical cyclization of alkenyl and alkynyl isonitriles, thus accomplishing the syntheses of pyridine and pyroglutamate derivatives.3k,f,j He also achieved the stereo-3 and enantioselective syntheses3k,m of (±)- and (−)-α-kainic acid through radical cascade reactions involving isonitriles bearing suitable unsaturated side chains.

Our long interest in the chemistry of imidoyl radicals4 recently led us to develop new synthetic strategies for the generation of those intermediates via radical addition to isonitriles. Quinoxaline derivatives have thus been synthesized by addition of cyano-substituted vinyl,4b alkyl,4c and sulfanyl4d radicals to aromatic isonitriles. Of special interest was our vinyl radical-mediated cyclo-penta-fused quinoxaline production,4f since it provided the first trimolecular version of the radical addition, tandem cyclization strategy. This finding seemed worthy of further investigations since three-component radical


    (g) Blum, P. M.; Roberts, B. P. J. Chem. Soc., Perkin Trans. 2 1978, 1313.
reactions, besides being quite rare, are potentially very powerful synthetic strategies. Indeed, they might provide access to polyfunctionalized molecules—or polyfunctional cyclic compounds—from very simple, easily accessible—often commercially available—starting materials.

In light of the fair propensity of vinyl radicals to add to isonitriles, we were prompted to exploit these reactions in search of other synthetically useful three-component procedures. Toward this purpose, the generation of vinyl radicals in the presence of isonitriles was carried out through regioselective addition of sulfanyl radicals to alkenes. Sulfonyl radicals in turn were produced by light-induced homolytic cleavage of the corresponding disulfides. The usual hydrogen abstraction from thiols was not considered, since thiols are known to be highly efficient scavengers of vinyl radicals. Here we are pleased to report that irradiation of aromatic disulfides in the presence of suitable alkenes and isonitriles can actually result in a novel three-component radical cascade reaction involving initial addition of a sulfanyl radical to the alkyne and subsequent addition of the ensuing vinyl radical to the isonitrile.

Results and Discussion

The first experiment was carried out by UV irradiation of a benzene solution (40 mL) of commercially available diphenyl disulfide 1a (0.5 mmol) and phenyleacetylene 2 (5 mmol) and easily accessible 4-methoxyphenyl isonitrile 3 (10 mmol). Benzene proved to be the best reaction solvent. Reactions carried out in methylene chloride, methanol, or hexane were characterized by lower yields and/or longer reaction times. Comparable yields but longer reaction times were obtained by performing the experiments in more concentrated solutions. Unexpectedly, the reaction afforded only products 4a, 5a, and 6, and derived from 1a and 2 without intervention of the isonitrile (Scheme 1, reaction a). This curious outcome, quite unpredictable in light of our previous results, led us to repeat the experiment in the presence of a radical scavenger to trap some reaction intermediate. Indeed, when the same reagents were allowed to react under identical conditions in the presence of m-dinitrobenzene (MDNB) we obtained again minor amounts of the above compounds together with amides 7 and 8 in ca. 60% overall yield (Scheme 1, reaction b). Structure 8 was assigned on the basis of the X-ray structure determined for another byproduct obtained from analogous, previously reported photolysis of disulfides and isonitriles. This result can be rationalized according to the reaction pathway shown in Scheme 2. Fast addition of a sulfanyl radical to the alkyne gives vinyl radical 9; subsequent addition of 9 to isonitrile 3 generates imidoyl radical 10. In the absence of MDNB, radical 10 cannot evolve rapidly into other intermediates; since the addition of 9 to 3 is likely to be reversible, it rather prefers to give back vinyl radical 9, which is responsible for the formation of compounds 4a, 5a, and 6. On the other hand, in the presence of MDNB, imidoyl 10 is efficiently trapped by...
the scavenger, giving the intermediate 11,14 fragmentation of 11 followed by hydrogen abstraction of amidyl radical 12 affords the final amide 7. An identical mechanism can explain the formation of amide 8 starting from sulfanyl radical 13, which is formed by ortho-selective photo-Fries rearrangement of the starting disulfide 1a.13

This result was particularly encouraging, since the reaction afforded—in fair overall yield—compounds derived from a selective three-component radical cascade reaction.15 In addition, the reaction provided a one-pot procedure for the synthesis of potentially interesting polyfunctionalized alkenes from three simple molecules. On this basis, we were prompted to explore the synthetic potential of this reaction by employing a different isonitrile, which might lead to an imidoyl radical capable of undergoing a fast evolution without the intervention of any additional fourth component (e.g., MDNB). The subsequent reactions were therefore carried out with commercially available tert-butyl isonitrile (14). Indeed, this is known to afford imidoyl radicals that undergo quite fast $\beta$-scission with release of a tert-butyl radical and formation of a nitrile.1a,b,2a-c,e,h-j,4g,16

When 1a (0.5 mmol), 2 (5 mmol), and 14 (10 mmol) were allowed to react under the usual conditions, the unsaturated nitrile 15a was produced in satisfactory yield (46%),17 in addition to minor amounts of compounds 4a (17%), 5a (2%), and 6 (21%) (Scheme 3). Nitrile 15a occurred as a mixture of the E- and Z-isomer, whose relative ratio was originally 4.5:1, but it became 6.7:1 upon chromatographic separation. The reaction mechanism is outlined in Scheme 4. As before, tandem addition of sulfanyl radical to phenylacetylene and reaction of the resulting vinyl radical with the isonitrile give imidoyl radical 16. This intermediate is efficiently "trapped" by $\beta$-fragmentation with loss of tert-butyl radical—a pathway that is precluded to imidoyl radical 10—and it is thus responsible for the formation of nitrile 15. Molecules with

(13) All of these compounds have been commonly observed in the reactions between sulfanyl radicals and phenylacetylene (see ref 6a,b). However, since we did not use thiols as a source of sulfanyl radicals, we were quite astonished to obtain the hydrogen-abstraction product 4a in significant amounts. In our reaction, one of the possible hydrogen-atom sources could be tentatively identified as the cyclohexadienyl radicals involved in the formation of compound 5a.

(14) For trapping of radicals by nitro groups resulting in oxygen-transfer reactions from the nitro moiety to the radical center, see, for example: Topiwala, U. P.; Luszniak, M. C.; Whiting, D. A. J. Chem. Soc., Perkin Trans. 1 1998, 1185.

(15) It is worth noting that the literature has reported several examples of both sulfanyl radical addition to isonitriles (see refs 2a,d,g and 4l) and imidoyl radical addition to alkynes (see ref 4a,c,h and: Dan-dh, Y.; Matta, H.; Uemura, J.; Watanabe, H.; Uneyama, K. Bull. Chem. Soc. Jpn. 1995, 68, 1497). Therefore, one could envisage an alternative reaction pathway including sulfanyl radical addition to 3 followed by reaction of the resulting $\alpha$-thio-imidoyl radical with 2 to give a vinyl radical. Cyclization of the latter intermediate onto the isonitrile aryl ring could lead to a quinoline derivative. Nevertheless, this kind of product was never observed under any experimental conditions.


(17) A large excess of isonitrile is essential to trap the vinyl radical efficiently. When we used 5 mmol of 14, the yield dropped to 15%.
natural or biologically active compounds.\textsuperscript{22} Considered a notable building block for a wide range of pull dienes for nonlinear optics applications,\textsuperscript{21} and it is fully employed in the syntheses of fungicides, herbicides, insecticides,\textsuperscript{19} cephalosporin derivatives,\textsuperscript{20} and push-pull dienes for nonlinear optics applications,\textsuperscript{21} and it is considered a notable building block for a wide range of natural or biologically active compounds.\textsuperscript{22}

a 15-like structure is potentially very interesting, since they combine the functionalities of α,β-unsaturated nitriles and vinyl sulfides, both of considerable importance in organic synthesis.\textsuperscript{18} Moreover, the specific skeleton of 15—a β-thio-substituted acrylonitrile—has been successfully employed in the syntheses of fungicides, herbicides, and insecticides,\textsuperscript{19} cephalosporin derivatives,\textsuperscript{20} and push-pull dienes for nonlinear optics applications,\textsuperscript{21} and it is considered a notable building block for a wide range of natural or biologically active compounds.\textsuperscript{22}

The reaction was repeated with various aromatic disulfides and alkynes (Table 1). The formation of nitrile 15 was favored by electron-withdrawing disulfide substituents: indeed, with R = CN or Cl a good yield of 15 (60%) was obtained. Furthermore, any R group was found to lower reaction times remarkably. This effect was particularly notable with disulfide 1b, whose reaction was about 10 times faster than that of disulfide 1a. Therefore, reactions with further alkynes were normally studied with disulfide 1b.

We first examined the use of trimethylsilylacetylene (17), which is known to react with sulfanyl to give vinyl radicals structurally analogous to those obtained with phenylacetylene.\textsuperscript{23} As shown in Scheme 5, in this case the formation of nitrile 21 was significantly hindered by the competing intramolecular ring closure of the vinyl radical to give benzothiophene 19. This behavior was somewhat expected, since α-trimethylsilyl−β-(phenylsulfanyl)vinyl radicals are reported to be much more prone to cyclize to benzothiophenes than α-phenyl−β-(phenylsulfanyl)vinyl radicals.\textsuperscript{6b}

The acrylonitrile 21 was produced as a 2.5:1 mixture of the geometrical isomers in 35% overall yield. However, column chromatography of the crude led to isolate only a 10% yield of a 1:1 mixture\textsuperscript{24} of (Z)-21 and (E)-21, together with a 25% yield of the starting disulfide 1b, which was initially shown by GC–MS analysis to be totally absent. Presumably, nitrile 21 was preferentially formed as the Z-isomer, which, under chromatographic conditions, could suffer extensive syn-elimination of transient aryl trimethylsilyl sulfide 22; this eventually gave disulfide 1b by subsequent decomposition (Scheme 6). The resulting stereochemistry of nitrile 21, as well as that of the above nitrile 15, can be explained in terms of preferential trapping of linear 1-trimethylsilyl- and 1-phenyl-2-(aryl-sulfanyl)vinyl radicals by isonitrile 14 on the side opposite to the sulfanyl moiety (see below for further discussion).

To test the possibility that the low yield of 21 could be a result of steric hindrance between the trimethylsilyl group of the vinyl radical and the tert-butyl substituent of the incoming isonitrile, we carried out the same reaction in the presence of an isonitrile bearing a linear side-chain, i.e., n-dodecyl isonitrile (24). Unexpectedly, after 9 h—the same time needed for complete disappearance of the starting material in the analogous reaction with 14—the reaction mixture contained major amounts of unreacted disulfide 1b and small quantities of 18 and 19: no trace of 21 was detected. Although not useful to throw more light on the reason 21 was obtained in low

---

\textsuperscript{24} In all of the reactions described in this paper, the alkene having the alkynel-derived group and the sulfanyl moiety on the same side of the C−C double bond is more stable than the other isomer. This was suggested by the silica-catalyzed isomerization observed during column chromatography and it was definitively proved by photoysis of each of the (supposed) less stable isomers in the presence of the corresponding disulfide. After 24 h under these conditions, they gave almost complete conversion to the alkene with the opposite configuration, due to reversible sulfanyl radical addition to the C−C double bond. See: (a) Rice, J. L. In Free Radicals; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. II, pp 720–724. (b) Oswald, A. A.; Griesbaum, K.; Hudson, B. E., Jr.; Bregman, J. M. J. Am. Chem. Soc. 1964, 86, 2877. (c) Kampaier, J. A.; Chen, G. J. Am. Chem. Soc. 1965, 87, 2608. (d) Heiba, E. I.; Dessau, R. M. J. Org. Chem. 1967, 32, 3837. It is worth noting that the most stable configuration is named E for the alkene obtained from phenylacetylene (and 1-heyne, see below) but Z for that arising from trimethylsilyleacetylene, due to the presence of the silicon atom instead of a carbon.
yields from 14, this finding interestingly gave additional support to the above postulated reversible attack of vinyl radicals to isonitriles. As a matter of fact, there is no plausible reason to postulate very different reaction rates between vinyl radical 23 and the two alkyl isonitriles 24 and 14. Even if we do, the fastest reaction should be that with 24 rather than the other one, since the linear side chain of 24 should minimize the steric hindrance in the transition state. Nevertheless, this reaction did not afford 21 at all. The only conceivable, meaningful difference between the two processes resides in the next step, i.e., the $\beta$-scission of the imidoyl radical, which furnishes either a tert-butyl—with 14—or a primary alkyl radical—with 24. Assuming a reversible addition step between vinyl radical 23 and the two isonitriles (Scheme 7), imidoyl radical 25 is rapidly consumed by the fast $\beta$-fragmentation with loss of a tert-butyl radical, thus driving the equilibrium toward nitrile 21. On the contrary, the $\beta$-scission of imidoyl 26, with loss of a primary carbon radical, cannot compete efficiently with the reverse reaction and the process exclusively affords 29 and in much longer times—products derived from vinyl radical 23. In our opinion, the overall present and previous results strongly suggest that radical addition to isonitriles is a reversible process, at least when—like in the case of vinyls 9 and 23—the attacking radicals possess a fair stability.

Much better results were obtained by reacting disulfide 1b and isonitrile 14 with 1-hexyne (27). This reaction afforded small amounts of byproducts 28 and 29 (3% each)—2,4-di-n-butylthiophene analogous to 6 and 20 was not detected at all—together with a good 50% yield of nitrile 30 (Scheme 8). In this case, a low yield of 29 was expected on the basis of the reported low propensity of $\alpha$-alkyl-$\beta$-(phenylsulfanyl)vinyl radicals to cyclize to benzothiophenes.\(^\text{4b}\)

Having shown that the three-component radical cascade reaction can be efficiently applied to alkynes with very different properties, in the next section we shall deal with a detailed mechanistic discussion about the stereochemical outcome of the reaction itself. As a matter of fact, the stereochemistry of the reactions of $\beta$-(arylsulfanyl)vinyl radicals with isonitriles differs significantly from the analogous reactions of those radicals with hydrogen donors.

First, let us summarize the results obtained with the three alkynes (Scheme 9). The reactions carried out with phenyl- (2) and trimethylsilylacetylene (17) afforded predominantly the alkenes arising from approach of the isonitrile to the side of the vinyl radical opposite to the sulfanyl group (E for the former and Z for the latter alkyne). Confining the discussion to alkyne 2 for sake of simplicity—the reaction with 17 suffers from decomposition problems of the major product—the two isomers were identified by mp and spectral data comparison between each of the two alkenes obtained in the reaction of disulfide 1d, partially separable by column chromatography, and authentic samples of compounds (E)-15d and (Z)-15d.\(^\text{25}\) Identification was then extended to products 15a–c on the basis of spectral analogies and assuming that no substantial change in the stereochemical outcome could be produced by changing the disulfide substituent. In addition, an NOE experiment was carried out on the presumed compound (E)-15c, which was unique to show sufficiently separated resonances in the aromatic region. By irradiating the two ortho protons of the $\alpha$-phenyl ring, we observed an exclusive positive effect on the signals of the two vicinal meta protons, whereas no effect at all was

noticed for the vinylic proton. The E/Z ratio increased slightly during the reaction, as proved by GC–MS analyses performed at regular times, and for compounds 15, it showed a remarkable enhancement after column chromatography (Scheme 9, values in parentheses).

The major production of the E-isomer was consistent with the results of previous reactions of a hydrogen donor with \( \beta \)-(arylsulfanyl)vinyl radicals.\(^{6a}\) \( \alpha \)-Phenylvinyl radicals have been suggested to be linear \( \pi \)-radicals,\(^{26}\) and to minimize steric hindrance, a hydrogen donor approaches an \( \alpha \)-phenyl-\( \beta \)-(arylsulfanyl)vinyl radical from the side trans to the sulfanyl moiety, yielding the corresponding alkene—under kinetic control—in a 1:9 E/Z ratio. This approach seems to be additionally favored by significant bonding interactions occurring between the unpaired electron and the sulfur orbitals.\(^{6a}\) This behavior should be substantially imitated also when the scavenger is an isonitrile and, as the isocyan group is at least as encumbering as the thiol group, we should expect for nitriles 15 an E/Z ratio of ca. 9:1 or even a little higher.\(^{27}\)

On the contrary, although we could not perform our reactions under perfect kinetic control, we can definitely say that in our case the E-isomer was actually still the major product, but the E/Z ratio was quite low, i.e., only 2.5–4.5:1. In addition, since for nitrile 15 the thermodynamically and kinetically favored isomers are the same compound (E)-15,\(^{24}\) the little isomerization that occurred during the reaction and altered the isomer ratio with respect to the one obtainable under kinetic control caused the E/Z ratio to increase rather than decrease. Therefore, we can reasonably conclude that, under absolute kinetic control, the E/Z ratio should be even lower than that observed and, thus, far away from what was expected.

Even more interesting were the results obtained from 1-hexyne 27. With this alkyne, the reaction is brought about by \( \alpha \)-alkyl-\( \beta \)-(arylsulfanyl)vinyl radicals, which—unlike the linear \( \alpha \)-phenyl-substituted analogues—are bent and rapidly interconverting \( \sigma \)-radicals.\(^{26}\) The choice of an incoming scavenger is again dictated by steric factors: if the reaction is dominated by the steric hindrance between the \( \alpha \)- and \( \beta \)-group of the vinyl radical, then a hydrogen donor enters on the same side of the sulfanyl group, giving the (E)-alkene; otherwise, it approaches the opposite side, yielding the Z-isomer. It is worth pointing out that with 27 the hydrogen-abstraction reaction follows the latter pathway affording the reduction product in a 1:9 E/Z ratio, thus perfectly resembling the result obtained with \( \alpha \)-phenyl-substituted vinyl radicals.\(^{6a}\) This means that also with 1-hexyne the product distribution is governed by steric interactions in the transition state between the \( \beta \)-substituent and the incoming scavenger. The negligible steric hindrance between the \( \alpha \)- and \( \beta \)-substituent of the vinyl radical, compared with that between the \( \beta \)-group and the isonitrile moiety, is also supported by the stability of compound (E)-30 that, like in the case of nitriles 15, is thermodynamically favored with respect to its (Z)-counterpart. This is an additional point that let us predict an approach of the isonitrile from the side opposite to the sulfanyl group.

As far as our reaction with 27 is concerned, the (E)-30/(Z)-30 ratio was not only low beyond any expectation, but, additionally, the kinetically favored product was (Z)-30 instead of the predicted (E)-isomer. As the matter of fact, when the reaction was stopped after 8 h, i.e., much before complete conversion of the starting material, the measured (E)-30/(Z)-30 ratio was 1:2.5. The ratio changed to 1:1.3 and 1:1 at the end of the reaction and after column chromatography, respectively, since—like in the case of the other nitriles—the E-isomer is the more stable and thence considerable Z/E isomerization occurred during the reaction and chromatographic separation. The assignment of the Z-structure to the kinetic product (the major isomer at early reaction times) was made on the basis of NOE measurements carried out on a pure sample of presumed (Z)-30 obtained after chromatographic work-up. Irradiation on the allylic methylene signals caused a marked enhancement of the vinyl proton.

Thus, the markedly decreased ratio of the (E)- and (Z)-nitriles 15 and the inversion of the expected stereochemistry for nitrile 30 clearly indicate that the scavenging of \( \beta \)-(arylsulfanyl)vinyl radicals by isonitriles and/or the stereochemical fate of the resulting imidoyl radicals are governed by more complicated factors than those involved in analogous hydrogen abstraction reactions.

The stereochemical outcome of our reactions might be explained in terms of possible vinyl radical–isonitrile interactions in the transition state. Since carbon radicals are well-known to attack intermolecularly the sulfur atom of aryl sulfides to give sulfunary radicals\(^{28}\) and isonitriles can be considered diradical species in their geminal radical acceptor/radical donor behavior—it would not be unreasonable to postulate that in the transition state the incoming isonitrile might interact not only with the vinyl-radical carbon but also with the sulfur atom (Scheme 10). This effect could direct the approach of the isonitrile to the same side of the sulfanyl group, thus partially balancing steric hindrance. Due to the significant intramolecular bonding interactions between the unpaired electron and the sulfur orbitals,\(^{6a}\) the three center interaction could be slightly important in the reactions of radical 9. On the contrary, this is likely to be quite significant in the case of radical 31, where the intramolecular overlap is instead unimportant. This hypothesis would lead to predict not only a low E/Z ratio for the alkene products in the reactions with phenylacetylene but also a marked preference for the Z-isomer with 1-hexyne, which is consistent with our experimental data.

A different approach to rationalize the product distribution is to consider the geometry and electronic structure of the imidoyl radical arising from addition of the vinyl radical to the isonitrile (Scheme 11). In the absence

---


(27) Calculations of both molar volume and parachor for thiol and isocyan group are well-known to attack intermolecularly the sulfur atom of aryl sulfides to give sulfunary radicals—isonitriles and/or the stereochemical fate of the resulting imidoyl radicals are governed by more complicated factors than those involved in analogous hydrogen abstraction reactions.

of significant interactions in the transition state other than steric hindrance, adduct 32 could be preferentially formed in its predicted E-configuration. Nevertheless, before undergoing β-fragmentation, (E)-32 might equilibrate to some extent to the Z-isomer through rotation around the virtually single Cβ-Cδ bond of the contributing resonance structure 33. Imidoyl radical (Z)-32 could be the thermodynamically preferred isomer due to some intramolecular bonding interactions between the unpaired electron and the sulfur orbitals, which should be even more effective than in vinyl radical 9 (see above). Very recently, some isoelectronic α,β-unsaturated acyl radicals 34 have been described in terms of analogous mesomeric structures (Scheme 11).29

Since no data have been so far reported concerning the geometry and electronic structure of α,β-unsaturated imidoyl radicals, semiempirical MNDO-d calculations were performed on radicals 32 (a: R = H, X = Ph; b: R = H, X = Me). Generally, imidoyls are α-radicals with a bent geometry at the radical center,24,31 but recent studies have suggested that—like in the case of the isoelectronic vinyl radicals26b,e—their geometry and delocalization degree of the unpaired electron may depend on the substitution pattern, i.e., the α-group and particularly the nitrogen substituent.32

Both energy and equilibrium geometry of radical (E)-32a were first optimized. The results shown in Scheme 12 indicate that a bent geometry (120°) at the radical center was transformed into a quasilinear arrangement (170.5°) of the N=C–C moiety. In addition, the order of the Cδ–Cb and Cβ–Cδ bonds was changed to 1.5 from 1 and 2, respectively, with the latter bond slightly longer than the former, however. Finally, the estimated spin density showed a maximum on the Cδ atom (0.40) instead of the starting Cα carbon (0.28), with some distribution also on the nitrogen (0.07) and sulfur (0.15) atoms. These data are more consistent with structure 33a rather than the initial imidoyl 32a. The energies and equilibrium geometries were then calculated for the other radicals (Z)-32a, (E)-32b, and (Z)-32b, and the rotation barriers were estimated for both pairs of radical configurations (6.0 and 5.7 kcal/mol, respectively, Scheme 13). Finally, from the kinetic data previously reported for β-fragmentations of analogous N-tert-butyl-substituted imidoyls,29 we estimated a value of ca. 8–10 kcal/mol for the activation energy concerning release of the tert-butyl

(30) The choice of MNDO-d parametrization was made to better take into account the possible involvement of sulfur d-orbitals.
radical from 32-like intermediates. On this basis, it can be reasonably assumed that, under our experimental conditions, radicals 32 can exhibit fair rotation around the C$_{6}^{-}$-C$_{7}$ bond, in competition with the $\beta$-scission process. The lower barrier predicted for radical 32b suggests that isomerization might be even more effective in the reaction carried out with 1-hexyne, which is consistent with the experimental data.

Although the above findings cannot afford a full explanation of the present stereochemical data, they strongly suggest that the structure of the $\alpha$-$\beta$-unsaturated imidoyl radical can have a major influence on the configuration of the reaction products and it can thence considerably alter the expected, kinetically favored outcome. However, at this stage, concomitant or even alternative contribution of transition state interactions (Scheme 10) cannot be ruled out.

It is worth pointing out that the above theoretical data also serve to clarify some as yet unexplained behavior of the related imidoyl radical 36. This was the key intermediate in the smooth formation of the cyclopenta-fused quinoxaline 38 (50% yield) by tandem 5-exo-dig cyclization onto the cyano group and subsequent six-membered ring closure of the resulting iminyl radical 37 onto the aromatic ring of the isonitrile (Scheme 14). At that time, we had no convincing explanation of the reasons why the radical intermediate 36 could undergo efficient cyclization on the nitrile moiety despite its kinetically predictable (and unfavorable) E-configuration. In light of the present data calculated for imidoyl radicals 32, ready E/Z isomerization of 36 through rotation around the C$_{6}^{-}$-C$_{7}$ bond—and thence approach of the radical center to the cyano group—now becomes plausible.

**Conclusions**

The photolytic reaction of disulfides with alkynes and isonitriles represents a novel three-component radical cascade reaction that proceeds by tandem addition of a sulfanyl radical to the alkyne and attack of the resulting vinyl radical to the isonitrile carbon atom to give an imidoyl radical. With aromatic isonitriles, a scavenger (e.g., MDNB) is needed to trap the produced imidoyl radical prior to back fragmentation to the vinyl precursor. With tert-butyl isonitrile, the imidoyl intermediate is "trapped" by a $\beta$-scission process resulting in release of a tert-butyl radical and production of a nitrile. This one-pot protocol affords fair yields of synthetically useful polyfunctionalized alkenes using disulfides, isonitriles, and alkynes with very different properties. Moreover, our present results suggest that vinyl radical addition to isonitriles is a reversible process: this fact is also supported by the reaction of disulfide 1b and alkyne 17 in the presence of a nonbranched aliphatic isonitrile (24).

The stereochemical outcome of the three-component reactions differs significantly from that previously encountered with related hydrogen abstraction reactions of thio-substituted vinyl radicals. This could be the consequence of vinyl radical–isonitrile interactions in the transition state and/or fast E/Z isomerization of the eventual imidoyl radical. Support to the latter possibility was given by structure and spin-density data obtained by MNDO-d semiempirical calculations.

**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. GC–MS analyses were carried out on a quadrupolar instrument equipped with a Quadrex capillary column (007, 25 m × 0.25 mm i.d.). The E/Z ratios for vinyl compounds were determined by a 60–260 °C temperature ramp with a rate of 10 °C/min, unless otherwise stated; the differences in retention times ($\Delta t$) are given in seconds. IR spectra were recorded in film or chloroform solution. Column chromatography was carried out on 60–230 mesh silica gel or basic alumina. 3) using light petroleum (40–70 °C) and a light petroleum/diethyl ether gradient (from 0 up to 100% diethyl ether) as eluant. UV photolyses of disulfides were performed with a Heraeus TQ 150 high-pressure mercury lamp (150 W). Previously reported reaction products were identified by spectral comparison and/or mixed mp determination with authentic specimens. The purity of new compounds was confirmed by HRMS and elemental analysis; in the case of inseparable mixtures of compounds, the purity was proved by the absence of any significant extraneous peak in the $^1$H NMR spectra and/or by GC–MS analysis.

Diphenyl disulfide (1a), 4-methoxythiophenol, 4-chlorothiophenol, 4-hydroxybenzonitrile, p-anisidine, N-dodecylamine, phenylacetylene (2), tert-butyl isonitrile (14), trimethylsilylacetylene (17), 1-hexyne (27), and m-dinitrobenzene (MDNB) were commercially available. 4-[4-(Cyanophenyl)disulfanyl]-
Radical Addition to Isonitriles

Siskin, M.

After removal of the solvent, the residue was chromatography of the reaction mixture afforded 345.0646, found 345.0658. The diphenylthiophene (4a) as a 4:1 E/Z mixture (2.5:1 before chromatography, 60% overall yield, \( \Delta_\text{m} = 30 \)): mp = 124−126 °C (from light petroleum/benzene 70:30 v/v); \( ^1 \)H NMR (200 MHz) 7.35−7.75 (m); \( ^1 \)C NMR (50 MHz) 122.41 (q), 126.60 (q), 118.35 (s), 128.65, 127.47 (q), 128.51, 129.47, 129.74, 129.98, 130.10, 130.52, 130.80, 132.34 (q), 133.53, 133.62, 139.15, 139.71 (s), 131.73, 134.56 Hz, 7.30 (1 H, bs, NH, removed upon treatment with D_2O), 7.40 (1 H, s), 7.30−7.85 (24 H, m), 8.34 (1 H, s); \( ^1 \)C NMR (50 MHz) 55.95, 114.65, 122.19, 122.27, 128.52, 129.04, 129.70, 129.83, 129.89, 129.93, 130.17, 130.31, 131.12, 131.14 (q), 131.50 (q), 131.60, 131.86 (q), 134.65 (q), 135.32 (q), 138.15 (q), 138.20 (q), 142.38, 145.43, 157.05 (q), 163.22 (q), 164.92 (q); MS m/z 361 (M−, 56); HRMS calc for C_{15}H_{11}NSO_3: C, 73.10; H, 5.30; N, 3.87; S, 8.87. 

Further elaboration was carried out on a fraction containing 3((4-methoxyphenyl)sulfanyl)-2-phenyl-2-propenamide (8) (0.05% yield) as a 3:1 mixture of stereoisomers; oil; 1H NMR (300 MHz) 6.40 (s, minor isomer), 4.04 (s, major isomer), 7.06−7.12 (d, 4 H, 8.22 Hz, J = 7.6 Hz, 7.25−7.90 (m)); MS m/z 267 (M+ 1971 J); further elaboration was carried out on a fraction containing 15c as a highly effective Z/E ratio by irradiating the two ortho protons of the unsubstituted \( \alpha \)-phenyl ring (7.87−9.93 ppm); the experiment showed an exclusive positive effect (35%) on the signals of the two vinylic meta protons (7−7.3 kHz), whereas no effect at all was noticed for the singlet attributable to the vinylic proton (7.29 ppm): MS m/z 267 (M+ 100); HRMS calc for C_{15}H_{11}NOS: C, 71.88; H, 4.90; N, 5.24; S, 11.99. Found: C, 72.05; H, 4.86; N, 5.26; S, 12.07.

A careful analysis of the final elution fractions showed that this reaction did not affect the photo-Fries rearrangement product.

Further elaboration was carried out on a fraction containing 15c as a highly effective Z/E ratio by irradiating the two ortho protons of the unsubstituted \( \alpha \)-phenyl ring (7.87−9.93 ppm); the experiment showed an exclusive positive effect (35%) on the signals of the two vinylic meta protons (7−7.3 kHz), whereas no effect at all was noticed for the singlet attributable to the vinylic proton (7.29 ppm): MS m/z 267 (M+ 100); HRMS calc for C_{15}H_{11}NOS: C, 71.88; H, 4.90; N, 5.24; S, 11.99. Found: C, 72.05; H, 4.86; N, 5.26; S, 12.07.

A careful analysis of the final elution fractions showed that this reaction did not affect the photo-Fries rearrangement product.

Further elaboration was carried out on a fraction containing 15c as a highly effective Z/E ratio by irradiating the two ortho protons of the unsubstituted \( \alpha \)-phenyl ring (7.87−9.93 ppm); the experiment showed an exclusive positive effect (35%) on the signals of the two vinylic meta protons (7−7.3 kHz), whereas no effect at all was noticed for the singlet attributable to the vinylic proton (7.29 ppm): MS m/z 267 (M+ 100); HRMS calc for C_{15}H_{11}NOS: C, 71.88; H, 4.90; N, 5.24; S, 11.99. Found: C, 72.05; H, 4.86; N, 5.26; S, 12.07.

A careful analysis of the final elution fractions showed that this reaction did not affect the photo-Fries rearrangement product.
(2, H, m) [lit. 25 H NMR (60 MHz) J 7.22–7.61 (m); one end of the resonance region is significantly shifted to lower fields for the E-isomer; this feature is clearly shown by the major isomer of 15d, see also below]; MS m/z 273 (M+ + 2, 25), 271 (M+, 100), 236 (26), 203 (52), 159 (32), 155 (16), 108 (22), 75 (31) [lit. 25 MS m/z 273 (M+ + 2, 36), 271 (M+, 100), 270 (29), 236 (40), 203 (58), 159 (24), 143 (29), 108 (29); Z; 15d: IR (film) 3365, 3000, 2920 (CN), 1500, 1480, 1450, 1400, 1100, 1015, 810, 750 (lit. 25 IR (KBr disk) cm−1) 2240 (CN), 1620; H NMR (300 MHz) J 7.35–7.52 (10 H, m) [lit. 25 H NMR (60 MHz) J 7.25–7.53 (m)]; MS m/z 273 (M+ + 2, 26), 271 (M+, 100), 236 (25), 203 (51), 159 (33), 155 (16), 108 (25), 75 (38) [lit. 25 MS m/z 273 (M+ + 2, 37), 271 (M+, 100), 270 (30), 236 (28), 203 (44), 159 (31), 155 (25), 139 (36), 108 (27)].

Final elution gave traces of the presumable 140 photo-Fries rearrangement product, 4-(4-chloro-2-(4-chlorophenyl)sulfanyl)phenyl)sulfanyl)-2-phenyl-2-propenitrile, MS m/z 413 (M+, 100); HRMS calc for C21H15ClNS2 412.9867, found 412.9875.

Reaction of 1b with 17 and 14. After 9 h, column chromatography of the reaction mixture afforded trimethyl-[4-(trimethylsilyl)-2-thienyl]silane 45 [MS m/z 228 (M+ + 13)]. Further elution gave a mixture of 18 and 19 in a 1:2 isomers in a 0.90:1 ratio; 3:5 ratio (26% overall yield, J 7.35 = 18); E-18; MS m/z 233 (M+, 23); Z-18; MS m/z 233 (M+, 20); HRMS calc for C13H15N2S 233.0776, found 233.0777; Z-18; MS m/z 231 (M+, 9); HRMS calc for C13H15N2Si 231.0695, found 231.0694; 2240 (CN), 1620; H NMR (300 MHz) J 7.35–7.52 (10 H, m) [lit. 25 H NMR (60 MHz) J 7.25–7.53 (m)]; MS m/z 273 (M+ + 2, 26), 271 (M+, 100), 236 (25), 203 (51), 159 (33), 155 (16), 108 (25), 75 (38) [lit. 25 MS m/z 273 (M+ + 2, 37), 271 (M+, 100), 270 (30), 236 (28), 203 (44), 159 (31), 155 (25), 139 (36), 108 (27)].

Further elution gave traces of the presumable photo-Fries rearrangement product, 4-[[2-cyano-1-hexenyl]sulfanyl]benzotriazole 30 as a 1:1.1 Z/E mixture (1:3.1 before chromatography). 2.5:1 if the reaction is stopped after 8 h, 50% overall yield, J 7.5 = 5; oil. (Z)-30; 1H NMR (300 MHz) J 0.95 (3 H, t, J = 7.2 Hz), 1.32–1.45 (2 H, m), 1.52–1.67 (2 H, m), 2.37 (2 H, t, J = 7.5 Hz, J 1 = 1.1 Hz), 6.90 (1 H, t, J = 1.1 Hz), 7.45 (2 H, A part of AA’BB’, J = 8.6 Hz), 7.65 (2 H, B part of AA’BB’, J = 8.6 Hz) MS m/z 242 (M+, 61). (E)-30; 1H NMR (300 MHz) J 0.98 (3 H, t, J = 6.8 Hz), 1.30–1.50 (2 H, m), 1.50–1.70 (2 H, m), 2.35 (2 H, br t, J = 6.8 Hz), 7.15 (1 H, t, J = 0.8 Hz), 7.40 (2 H, A part of AA’BB’, J = 8.5 Hz), 7.65 (2 H, B part of AA’BB’, J = 8.5 Hz); MS m/z 242 (M+, 61). HRMS calc for C14H14N2S (E/Z mixture) 242.0878, found 242.0883. Analysis calc for C14H14N2S (E/Z mixture): C, 69.39; H, 5.82; N, 11.56; S, 13.23. Found: C, 69.32; H, 5.79; N, 11.60; S, 13.30. A NOEDIF experiment was carried out on a fragment containing J 7.30 by irradiating the two allylic protons (2.37 ppm); the experiment showed an exclusive positive effect (2%) on the signal of the vinyllic proton (6.90 ppm).

Final elution gave traces of the presumable photo-Fries rearrangement product, 4-[[2-cyano-1-hexenyl]sulfanyl]trithienyl]silane 32a (M+ + 28); [minor]; 375 (M+, 100); HRMS calc for C21H15N2S (E/Z mixture) 375.0864, found 375.0879.

Siempirical Calculations. Semiempirical calculations on radicals (E)-32a.b and (Z)-32a.b were carried out by using the CS MOPAC routine included in the CambridgeSoft ChemOffice Pro 4.0 package. After a careful conformational search, the geometries of the open-shell intermediates were fully optimized following the MNDO-d parameterization. Geometries and energies for radicals (E)-32a.b and (Z)-32a,b are shown in Schemes 12 and 13. The rotation barrier for each couple of intermediates (Scheme 13) was calculated by determining the maximum of the energy profile for rotation of the C–C bond; this was obtained by calculating single point energies for a series of intermediates with decreasing C–C–C–C–S dihedral angles.

Acknowledgment. We gratefully acknowledge financial support from CNR, MURST (1998–1999 Grant for “Free Radicals and Radical Ions in Chemical and Biological Processes”), and the University of Bologna (1997–1999 Funds for Selected Research Topics). We also thank Dr. Alessandro Mezzetti for the experimental work.

Supporting Information Available: Full IR and MS data for compounds 4b, 5b, c, 7, 8, 15a–c, 18, 19, 21, 28–30, and 40 and photo-Fries rearrangement products. This material is available free of charge via the Internet at http://pubs.acs.org.

J O991871Y


(46) A GC–MS analysis showed the presence of trace amounts of another isomer with m/z 231, whose structure was not investigated [MS m/z 231 (M+, 25), 216 (100), 200 (2), 186 (9), 176 (17), 140 (16), 114 (9), 108 (15)].