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Synthesis of Carbocyclic and Heterocyclic Fused Quinolines by Cascade Radical Annulations of Unsaturated *N*-Aryl Thiocarbamates, Thioamides, and Thioureas

Wu Du and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

curran@pitt.edu

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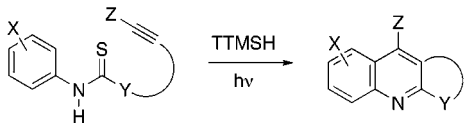
ABSTRACT



Tandem radical cyclizations of suitably substituted *N*-aryl thiocarbamates, thioamides, and thioureas are induced by exposure to *tris*(trimethylsilyl)-silane (TTMSH) and UV light and provide furoquinolines, isofuroquinolines, cyclopentaquinolines, indoloquinolines, and related ring systems. The intermediacy of an α-thioalkylamino radical, which is the synthetic equivalent of an imidoyl radical, is invoked.

Annulation reactions of imidoyl radicals **1** provide powerful ways to make an assortment of fused quinolines **2** (Figure 1).[1−3] In turn, these imidoyl radicals can be formed either by radical additions to isonitriles or from imidoyl halides and related radical precursors.[4] α-Thioaminoalkyl radicals **4** should be readily available from thioamides **3**, and they can be considered as synthetic equivalents of imidoyl radicals **1** since elimination of the thiol may occur either during or after cascade reactions of **4**. Bachi pioneered the use of such radicals to make assorted heterocycles in the early 1990s.[5] Fukuyama's two recent indole syntheses provide striking examples of the power of radical cyclizations of both imidoyl radicals and their equivalent α-thioaminoalkyl radicals.[6]

In this Letter, we show that cascade radical annulations of readily available thiocarbamates **5a**, thioamides **5b**, and thioureas **5c** provide direct routes to carbocyclic and heterocyclic fused quinolines **6a**−**c** (Scheme 1). These reactions complement existing imidoyl radical methods by making the same products from different precursors. More importantly, they also provide access to products that are not readily made through imidoyl radical chemistry either

(1) Johnson, C. D. In *Rodd's Chemistry of Carbon Compounds*; Sainsbury, M., Ed.; Elsevier: Amsterdam, 1998; Vol. IV, pp 129−161.

(2) (a) Josien, H.; Ko, S. B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67−83. (b) de Frutos, O.; Curran, D. P. *J. Comb. Chem.* **2000**, *2*, 639−649. (c) Curran, D. P.; Josien, H.; Bom, D.; Gabarda, A.; Du, W. In *The Camptothecins: Unfolding their Anticancer Potential*; Liehr, J. G., Giovanella, B. C., Verschraegen, C. F., Eds.; New York Academy of Sciences: New York, 2000; Vol. 922. (d) Gabarda, A. E.; Du, W.; Isarno, T.; Tangirala, R. S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 6329−6341. (e) Luo, Z. Y.; Zhang, Q. S.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766−1769. (f) Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215−3218.

(3) (a) Nanni, D.; Pareschi, P.; Rizzoli, C.; Sgarabotto, P.; Tundo, A. *Tetrahedron* **1995**, *51*, 9045−9062. (b) Nanni, D.; Pareschi, P.; Tundo, A. *Tetrahedron Lett.* **1996**, *37*, 9337−9340. (c) Leardini, R.; Nanni, D.; Pareschi, P.; Tundo, A.; Zanardi, G. *J. Org. Chem.* **1997**, *62*, 8394−8399. (d) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G. *Tetrahedron Lett.* **1998**, *39*, 2441−2442. (e) Nanni, D.; Calestani, G.; Leardini, R.; Zanardi, G. *Eur. J. Org. Chem.* **2000**, 707−711. (f) Leardini, R.; Nanni, D.; Zanardi, G. *J. Org. Chem.* **2000**, *65*, 2763−2772.

(4) Reviews: (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177−194. (b) Nanni, D. In *Radicals in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 44−61. (c) Zard, S. Z. In *Radicals in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, pp 91−108.

(5) (a) Bachi, M. D.; Bosch, E. *J. Org. Chem.* **1992**, *57*, 4696−4705. (b) Bachi, M. D.; Balanov, A.; Barner, N.; Bosch, E.; Denenmark, D.; Mizhiritskii, M. *Pure Appl. Chem.* **1993**, *65*, 595−601.

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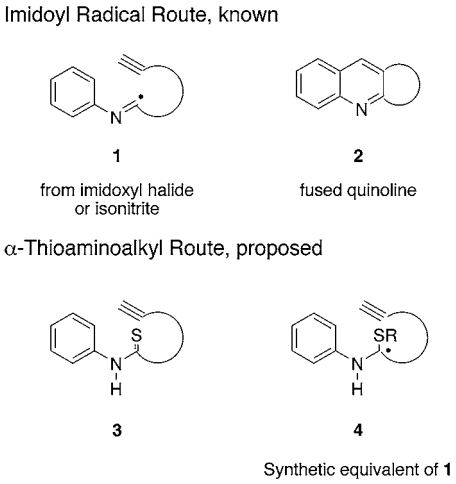
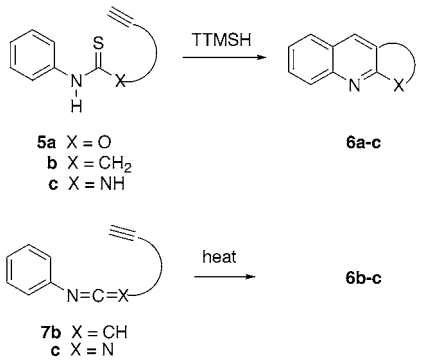


Figure 1. Imidoyl radical and α-thioaminoalkyl radical routes to fused quinolines.

because the needed imidoyl radical precursors are not available or not stable or because the requisite radicals do not add cleanly to isonitriles. Fused quinolines **6b** and **6c**

Scheme 1



can also be made by thermal cyclizations of ketene imines[7] **7b** or carbodiimides **7c**.[8] These reactions were originally formulated as intramolecular Diels−Alder reactions and more recently as diradical electrocyclizations.[9] The direct route to **6b**,**c** reported herein bypasses the formation of the sensitive

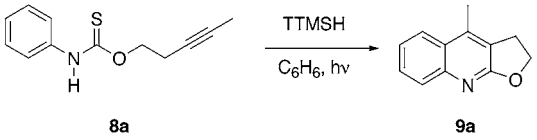
(6) (a) Fukuyama, T.; Chen, X. Q.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127−3128. (b) Kobayashi, Y.; Fukuyama, T. *J. Heterocycl. Chem.* **1998**, *35*, 1043−1055. (c) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791−3792. (d) Reding, M. T.; Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *Heterocycles* **2002**, *56*, 313−330. (e) Rainier, J. D.; Kennedy, A. R.; Chase, E. *Tetrahedron Lett.* **1999**, *40*, 6325−6327. (f) Rhee, J. U.; Bliss, B. I.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2003**, *125*, 1492−1493.

(7) Differding, E.; Ghosez, L. *Tetrahedron Lett.* **1985**, *26*, 1647−1650.

(8) Molina, P.; Alajarin, M.; Vidal, A.; Sanchez-Andrada, P. *J. Org. Chem.* **1992**, *57*, 929−939.

(9) (a) Schmittel, M.; Steffen, J.-P.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2371−2373. (b) Schmittel, M.; Steffen, J.-P.; Angel, M. A. W.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1562−1564. (c) Shi, C.; Zhang, Q.; Wang, K. K. *J. Org. Chem.* **1999**, *64*, 925−932.

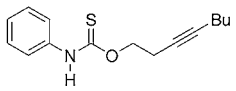
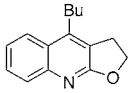
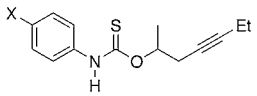
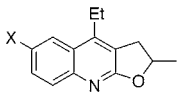
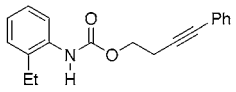
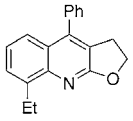
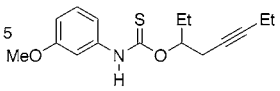
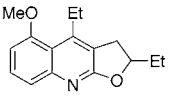
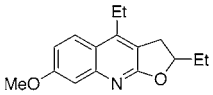
Scheme 2



and reactive ketene imine (**7b**) or carbodiimide (**7c**) intermediates.

We initially focused on identifying reaction conditions to convert phenylcarbamic acid pent-3-ynyl ester **8a** into known 4-methyl-2,3-dihydrofuro[2,3-*b*]quinoline **9a**.[10] Thiocarbamate **8a** was readily prepared by reaction of 4-pentyn-1-ol with phenyl isothiocyanate promoted by NaH.[11] Heating or irradiating **8a** in the presence of tributyltin hydride or hexamethylditin (typical conditions for cascade isonitrile annulations[2]) provided little or no furoquinoline **9a**. Substituting with tristrimethylsilyl silane[12] (TTMSH) gave better results, and standard conditions involved UV irradiation of a 0.05 M solution of **8a**, AIBN (1 equiv), and TTMSH (4 equiv) in benzene in a Pyrex test tube. After 20 h, the

Table 1. Cyclizations of Thiocarbamates[a]

Entry	Substrate	Product	Yield [b]
1	 **8b**	 **9b**	44%
2	 **8c** X = H	 **9c** X = H	47%
3	**8d** X = OMe	**9d** X = OMe	67%
4	 **8e**	 **9e**	88%
5	 **8f**	 **9f** +  **9f'**	1.3/1 67%

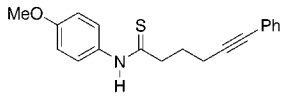
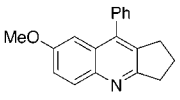
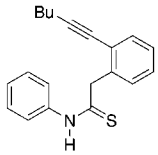
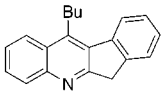
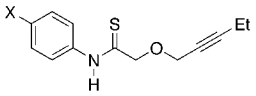
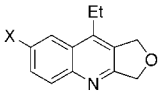
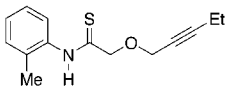
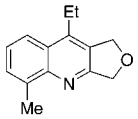
[a] Reaction conditions: C_6H_6, 4 equiv of TTMSH, 20 h, irradiation. [b] Isolated yield.

reaction mixture was concentrated and the crude product was purified by flash chromatography to provide **9a** in 48% yield.

Five other *N*-aryl thiocarbamates were prepared and cyclized in a similar fashion, and the results of this series of experiments are summarized in Table 1. Isolated yields of furoquinolines **9b**−**f** ranged from 44 to 88%. The *N*-aryl thiocarbamates **8d** and **8e** with substituents in the ortho and para positions, respectively, provided a single regioisomeric product **9d** or **9e** (entries 3 and 4), while the thiocarbamate **8f** with a *meta*-substituent provided two regioisomers **9f**/**9f**″ in a ratio of 1.3/1. This lack of regioselectivity for *meta*-substituted systems is typical for related cascade radical annulations of isonitriles.[2,3]

Thioamides also undergo cyclizations under the standard conditions as shown by the six examples in Table 2.

Table 2. Cyclizations of Thioamides[a]

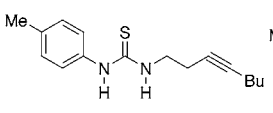
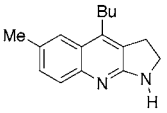
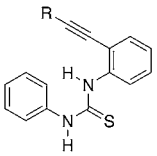
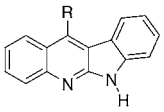
Entry	Substrate	Product	Yield[b]
1	 **10a**	 **11a**	87%
2	 **10b**	 **11b**	52%
3	 **10c** X = H	 **11c**	67%
4	**10d** X = OMe	**11d**	50%
5	**10e** X = F	**11e**	53%
6	 **10f**	 **11f**	62%

[a] Reaction conditions: C_6H_6, 4 equiv of TTMSH, 20 h, irradiation. [b] Isolated yield.

Cyclization of standard thioamide **10a** provided 2,3-dihydro-1*H*-cyclopenta[*b*]quinoline **11a** in 87% yield (entry 1). This can also be prepared by reaction of *p*-methoxyphenylisonitrile with the appropriate pentynyl radical precursor.[13] The cyclization of benzylthioamide **10b** gave 6*H*-indeno[2,1-*b*]-quinoline **11b** in 52% yield (entry 2). Cyclizations of four α-propargyloxy thioamides **10c**−**f** gave the unusual 1,3-dihydrofuro[3,4-*b*]quinolines **11c**−**f**, respectively, in moderate yields (50−62%, entries 3−6).

Finally, cyclizations of three thioureas were tried with mixed results, as summarized in Table 3. Attempts to cyclize

Table 3. Cyclizations of Thioureas[a]

Entry	Substrate	Product	Yield[b]
1	 **12a**	 **13a**	n.d.[c]
2	 **12b** R = Ph	 **13b**	64%
3	**12c** R = Bu	**13c**	47%

[a] Reaction conditions: C_6H_6, 4 equiv of TTMSH, 20 h, irradiation. [b] Isolated yield. [c] nd = not detected.

N-homopropargyl thiourea **12a** under the standard conditions or other variants were not successful (entry 1); however, *N*-(*o*-propargylaryl) thioamides **12b** and **12c** both underwent clean cyclizations to give indoloquinoline derivatives **13b**[9c,14] and **13c** in 64 and 47% yields, respectively (entries 2, 3). Indoloquinolines exhibit a diverse assortment of biological activities,[15] and this new approach opens the door to preparation of new members of this family.

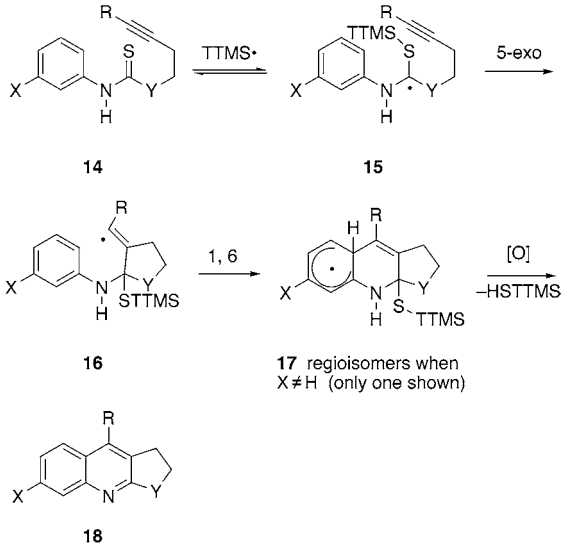


Figure 2. Suggested mechanism for thiocarbamate (Y = O), thioamide (Y = CR_2), and thiourea (Y = NR) cyclizations.

(10) Shanmugam, P.; Lakshminarayana, P.; Palaniappan, R. *Monatsh. Chem.* **1973**, *104*, 633−639.

(11) Preparations of this precursor and all the others in Tables 1−3 are described in Supporting Information.

(12) Chatgilialoglu, C.; Ferreri, C.; Gimisis, T. In *Chemistry of Organic Silicon*; Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, UK, 1998; Vol. 2, pp 1539−1579.

We posit the mechanistic framework in Figure 2 to interpret the results of these reactions. Reversible addition of the TTMS radical to the thiocarbonyl group of **14** gives stabilized radical **15**, which undergoes cyclization to vinyl radical **16**. Now 1,6-cyclization to one of the vacant ortho sites provides delocalized radical **17**. From here, oxidative rearomatization[16] is followed by ionic loss of the thiol.[17] The failure of the *N*-homopropargyl analogue **12a** to participate in this annulation may be because radical **15** with Y = *N*-alkyl is too stable.[5] The mixture of regioisomers formed from *meta*-substituted precursors such as **8f** arises because there are two vacant ortho sites on radical **16**. Ipso cyclization of **16** is also possible and sometimes occurs in related imidoyl radical cascades.[2,3] But the results to date suggest that it does not occur in thiocarbonyl cascades because ipso cyclization is postulated to lead to rearranged products,[2,3] and we have not yet isolated any such products.

These radical annulations of thiocarbamates, amides, and ureas supplement the related reactions of imidoyl radicals generated either from standard radical precursor or by additions to isonitriles. Likewise, they shortcut pericyclic and electrocyclic routes to these compounds since the formation of high energy cumulenes is not needed. Accordingly, radical annulations of thiocarbamates, amides and ureas show excellent potential for making a wide assortment of fused quinolines both rapidly and efficiently.

Acknowledgment. We thank the National Institutes of Health for funding this work. Wu Du thanks the University of Pittsburgh for a Mellon Predoctoral Fellowship.

Supporting Information Available: Typical procedure and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0344319

(13) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127−2132.
(14) Marsili, A. *Tetrahedron* **1968**, *24*, 4981−4991.
(15) (a) Peczynska-Czoch, W.; Pognan, F.; Kaczmarek, L.; Boratynski, J. *J. Med. Chem.* **1994**, *37*, 3503. (b) Kaczmarek, L.; Peczynska-Czoch, W.; Osiadacz, J.; Mordarski, M.; Sokalski, W. A.; Boratynski, J.; Marcinkowska, E.; Glazman-Kusnierczyk, H.; Radzikowski, C. *Bioorg. Med. Chem.* **1999**, *7*, 2457.
(16) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119−10128.
(17) Resulting thiol is a precursor of a thio radical, which in turn may add to the starting C=S bond to initiate a cyclization. Chatgilialoglu, H.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991−2069.