

# Thiol-mediated radical cyclization: regioselective formation of indole-annulated sulfur heterocycles by tandem cyclization

K. C. Majumdar,\* P. Debnath, S. Alam and P. K. Maji

Department of Chemistry, University of Kalyani, Kalyani 741 235, West Bengal, India

Received 27 May 2007; revised 7 July 2007; accepted 20 July 2007

Available online 27 July 2007

**Abstract**—Indole-2-yl-prop-2-ynyl sulfides, under thiophenol-mediated alkenyl radical cyclization conditions, afforded exclusively 4-thiophenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles or 3-thiophenylmethyl-2,3,8-trihydrothieno[2,3-*b*]indoles depending on the substituent at the indole nitrogen.

© 2007 Elsevier Ltd. All rights reserved.

Radical reactions have become a useful tool in synthetic organic chemistry.<sup>1</sup> The synthesis of sulfur heterocycles<sup>2</sup> by radical reactions present a major challenge in organic synthesis. The most common mediator of radical reactions in synthetic organic chemistry is tributyltin hydride.<sup>1</sup> Naito et al.<sup>3,4a</sup> have recently explored a new, efficient carbon–carbon bond forming reaction based on sulfanyl radical addition–cyclization. These radical reactions proceed via formation of a carbon-centred radical species generated by the addition of a sulfanyl radical to an unsaturated bond and subsequent intramolecular addition of the resulting carbon-centred radical to another multiple bond. Intermolecular addition of a radical to terminal alkynes offers an attractive tactic for the generation of alkenyl radicals and thiophenol<sup>2a,4</sup> is a very efficient reagent for this purpose. Moreover, the cyclized products are functionalized with a phenylthio moiety and thus are regarded as useful intermediates for further transformation.<sup>3a,4b</sup> In our present study, we focused on the thiophenol-mediated radical reaction for the construction of indole-annulated sulfur heterocycles. Here, we report the results of our investigation.

The required precursors indole-2-yl-prop-2-ynyl sulfides **3a–d** were synthesized in 90–95% yields by the reaction of various substituted indoline-2-thiones **1a–d** and propargyl bromide **2** under phase transfer catalysis

conditions using benzyltriethylammonium chloride (BTEAC) as phase transfer catalyst (Scheme 1).

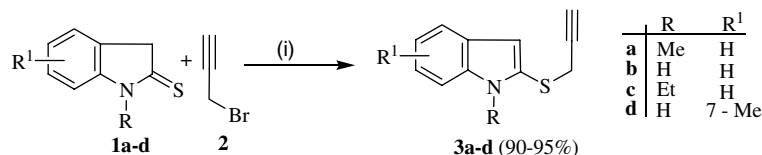
In an attempt to prevent the *thio*-Claisen rearrangement<sup>5</sup> the sulfides were purified at room temperature. Sulfide **3a** was treated with PhSH (2 equiv) in refluxing *tert*-butanol in the presence of a radical initiator (AIBN, 1.5 equiv) for 20 min. A colourless solid **4a**, mp 104 °C was obtained in 82% yield (Scheme 2). The same product was also obtained when the reaction was carried out in refluxing benzene. However, the *thio*-Claisen rearrangement product<sup>5</sup> **6**, under similar reaction conditions did not give any of the expected product even after 5 h.

The structure of **4a** was confirmed by single crystal X-ray diffraction<sup>6</sup> (Fig. 1) and was characterized as 9-methyl-4-thiophenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole.

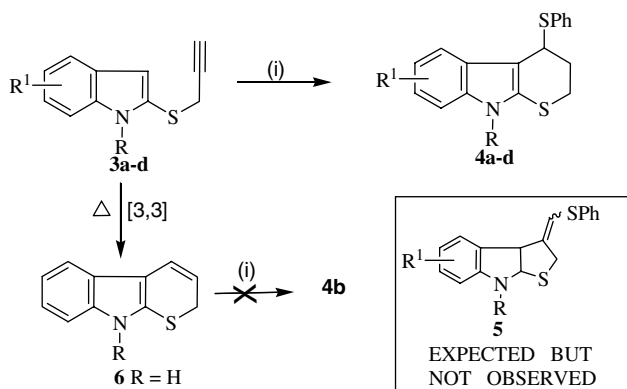
Substrates **3b–d**, under similar treatment gave the products **4b–d** in 76–80% yields. The reaction was also successfully conducted with thiophenol (1 equiv) and acetic acid in refluxing *t*-butanol. Substrate **3a**, in *tert*-butanol in the presence of AIBN (1 equiv), acetic acid (0.5 equiv) and thiophenol (1 equiv) afforded the same product **4a** in a lower yield (58%). However, in the absence of AIBN substrate **3a** failed to give any product due to extensive decomposition. In the case of alkenyl radical cyclizations of **3** the formation of products **4** are unusual. The reductive addition of a thiophenyl radical at the alkyne terminus can generate alkenyl radical **7**. It should be noted that the initially generated alkenyl radical **7** could undergo either 4-*exo-trig* or 5-*endo-trig*

**Keywords:** Thiophenol; Indoline-2-thione; Tandem cyclization; Regioselectivity.

\* Corresponding author. Tel.: +91 33 25827521; fax: +91 33 2582 8282; e-mail: [kcm\\_ku@yahoo.co.in](mailto:kcm_ku@yahoo.co.in)

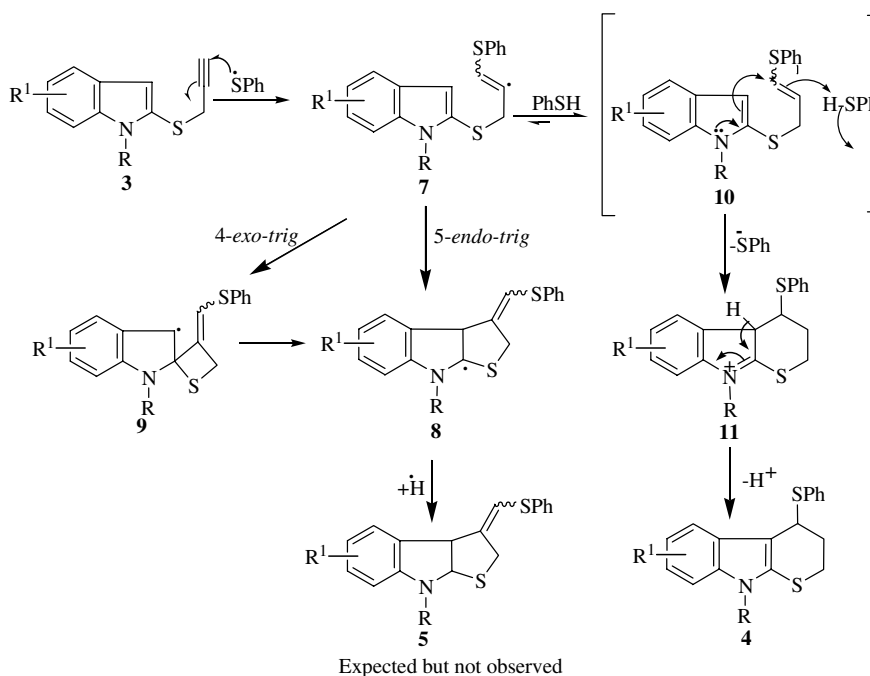


Scheme 1. Reagents and conditions: 1% NaOH, DCM, BTEAC, rt, 15 min.



Scheme 2. Reagents and conditions: (i) *t*-butanol, PhSH, AIBN, reflux, 20–25 min.

cyclization. A 5-*endo-trig* cyclization of radical **7** produces the intermediate radical **8** whilst a 4-*exo-trig* cyclization gives the spiroheterocyclic radical **9** followed by neophyl rearrangement<sup>7</sup> to radical intermediate **8**. The formation of products **4** from **3** is explicable by abstraction of a hydrogen radical by the intermediate radical **7** to afford intermediate **10** followed by intramolecular addition of enamine (indole or indole with electron donating group) to thioether ether via an ionic pathway. This is possible due to the availability of a nitrogen lone pair (Scheme 3).



Scheme 3.

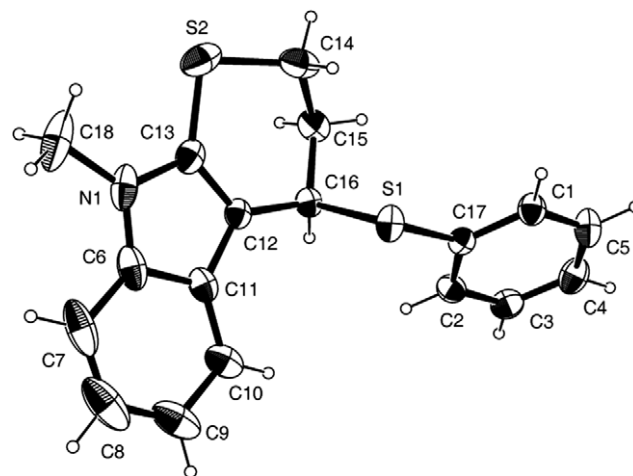
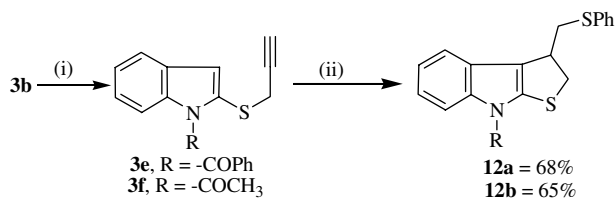


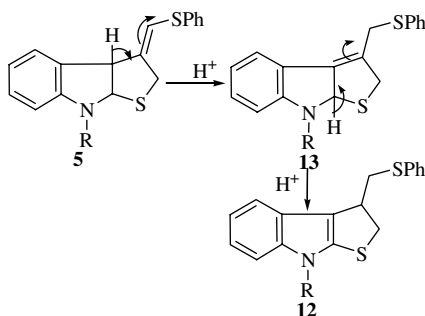
Figure 1. ORTEP diagram of **4a**.

With a view to investigate the participation of the lone pair of nitrogen of the indole moiety in the cyclization we prepared substrates **3e,f** by reaction of compound **3b** with benzoyl chloride or acetyl chloride, respectively (Scheme 4).

Compound **3e** was treated as in the case of compounds **3a–d** to afford product **12a** in 68% yield. It was characterized as 3-thiophenylmethyl-8-benzoyl-2,3,8-trihydrothi-



**Scheme 4.** Reagents and conditions: (i) PhCOCl or CH<sub>3</sub>COCl dry DCM, Bu<sub>4</sub>NHSO<sub>4</sub>, NaOH (powdered), stirring, 1 h, 0 °C; (ii) *t*-butanol, PhSH, AIBN, reflux, 25 min.



**Scheme 5.**

eno[2,3-*b*]indole. Compound **3f**, on similar treatment, gave product **12b** in 65% yield (Scheme 4). Thus, when electron withdrawing groups are attached at the indole nitrogen, the pyrrole ring of indole becomes much less aromatic and hence more alkene-like, thereby facilitating the radical cyclization to form **5** (Scheme 3) followed by two successive proton exchanges to afford products **12** (Scheme 5). Aromatization of the indole moiety may be the driving force for the formation of products **12** from **5**.

In conclusion, 4-thiophenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole was formed via initial intermolecular attack of a thiophenyl radical at the acetylenic sulfide followed by hydrogen abstraction and intramolecular addition of enamine to thioenol ether. The lone pair of electrons present on the nitrogen atom of the indole moiety may facilitate enamine addition, which leads to the formation of six-membered thiopyrano products **4**. However, in the presence of electron withdrawing groups on the nitrogen of the indole moiety, 5-*endo-trig* radical cyclization of the alkenyl radical becomes facile and 3-thiophenylmethyl-2,3,8-trihydrothieno[2,3-*b*]indoles were obtained. The methodology described here is simple and mechanistically interesting.

### Acknowledgements

We thank the CSIR (New Delhi) for financial assistance. We thank Professor A. Srikrishna, Indian Institute of Science, Bangalore, for helpful discussions and Professor A. T. Khan, Indian Institute of Technology, Guwahati, for the XRD data of **4a**. Two of us (S.A. and P.K.M.), and one of us (P.D.), are thankful to UGC (New Delhi) and the CSIR, respectively, for senior research fellowships. We thank the DST (New Delhi) for providing UV–vis and IR spectrometers under the FIST program.

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.132.

### References and notes

- (a) Majumdar, K. C.; Alam, S. *Org. Lett.* **2006**, *8*, 4059; (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 715–779; (c) Fossey, J.; Lefort, D.; Sorba, J. *Free radicals in Organic Synthesis*; Wiley: Chichester, 1995; (d) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992; (e) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2004**, *60*, 6239; (f) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2005**, *61*, 10603.
- (a) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. *Org. Lett.* **2003**, *5*, 1313; (b) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2006**, *71*, 3192; (c) Benati, L.; Capella, L.; Montevocchi, P. C.; Spagnolo, P. *J. Org. Chem.* **1995**, *60*, 7941; (d) Della, E. W.; Graney, S. D. *Tetrahedron Lett.* **2000**, *41*, 7987; (e) Della, E. W.; Graney, S. D. *Org. Lett.* **2002**, *4*, 4065; (f) Majumdar, K. C.; Biswas, A.; Mukhopadhyay, P. P. *Synthesis* **2003**, 2385; (g) Majumdar, K. C.; Mukhopadhyay, P. P.; Biswas, A. *Tetrahedron Lett.* **2005**, *46*, 6655.
- (a) Miyata, O.; Muroya, K.; Kobayashi, Y.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459; (b) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.; Naito, T. *J. Org. Chem.* **2002**, *65*, 6922; (c) Miyata, O.; Kajisa, S.; Ueda, M.; Yamauchi, M.; Naito, T. *Chem. Pharm. Bull.* **2005**, *53*, 995; (d) Miyata, O.; Yamanaka, K.; Ueda, M.; Naito, T. *Arkivoc* **2003**, *viii*, 220; (e) Miyata, O.; Nakajima, E.; Naito, T. *Chem. Pharm. Bull.* **2001**, *49*, 213; (f) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199; (g) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 19.
- (a) Miyata, O.; Naito, T. *C.R. Acad. Sci. Paris Chem.* **2001**, *4*, 401; (b) Lachia, M.; Denes, F.; Beaufils, F.; Renaud, P. *Org. Lett.* **2005**, *7*, 4103; (c) Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612; (d) Capella, L.; Montevcehi, P. C.; Navacehia, M. L. *J. Org. Chem.* **1996**, *61*, 6783; (e) Harrowven, D. C.; Maj, P. J.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 503; (f) Martinez-Grau, A.; Curran, D. P. *Tetrahedron Lett.* **1997**, *53*, 5679; (g) Burke, S. D.; Jung, K. W. *Tetrahedron Lett.* **1994**, *35*, 5837; (h) Beaufils, F.; Denes, F.; Renaud, P. *Org. Lett.* **2004**, *6*, 2563; (i) Fernandez, M.; Alonso, R. *Org. Lett.* **2005**, *7*, 11.
- Takada, S.; Makisumi, Y. *Chem. Pharm. Bull.* **1984**, *32*, 872.
- X-ray crystallographic data of **4a**: CCDC reference no: CCDC-653244. C<sub>18</sub>H<sub>17</sub>NS<sub>2</sub>, *M*: 311.45; monoclinic; space group *P2(1)/c*; unit cell dimensions: *a* = 9.0370(9) Å, *b* = 16.9899(18) Å, *c* = 10.4114(11) Å,  $\alpha$  = 90°,  $\beta$  = 98.630(6)°,  $\gamma$  = 90°. *Z* = 4, *D*<sub>calcd</sub> = 1.309 Mg/m<sup>3</sup>, *F*(000) = 656, *R*<sub>1</sub> = 0.0443, *wR*<sub>2</sub> = 0.1009, *R*<sub>1</sub> = 0.0827, *wR*<sub>2</sub> = 0.1178 (all data).
- Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072.