

Thiol mediated 8-*endo*-trig radical cyclization: an easy access to medium-sized cyclic ethers

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Abstract—An efficient new method for the synthesis of eight-membered heterocycles has been developed via a thiophenol mediated intramolecular 8-*endo* radical cyclization reaction. Alkenyl radicals are generated from easily available terminal alkynes and thiophenol.

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1. Introduction

Several methods¹ have been developed for the construction of medium-sized oxacycle rings including ring-closing metathesis (RCM). Recently, radical cyclization reactions have been developed as a potential method for the synthesis of various types of cyclic compounds via intramolecular carbon–carbon bond forming processes.² Much attention has been paid to the construction of five- and six-membered rings by radical cyclization.² However, there are problems associated with the formation of medium-sized rings using the aforesaid protocol. Several authors were able to prepare seven-membered ring systems using a tin hydride-mediated 7-*endo*-trig cyclization strategy.³ There are few examples in the literature for the construction of eight-membered ring systems by radical cyclization.⁴ Recently, Roy et al.⁵ described titanocene(III) mediated 8-*endo* radical cyclization for the synthesis of eight-membered cyclic ethers. Naito et al.^{6,7a} have explored a new, efficient carbon–carbon bond forming reaction based on sulfanyl radical addition and cyclization. These radical reactions proceed via the formation of a carbon-centered radical species generated by the addition of a sulfanyl radical to an unsaturated bond, followed by intramolecular addition of the resulting carbon-centered radical to a multiple bond. Thiophenol⁷ is a very effi-

cient reagent for this purpose. Moreover, during the cyclization process, a phenylthio moiety is incorporated into the final cyclized products. This functionalization is particularly attractive for further transformation of the products.^{6a,7b} To the best of our knowledge, only one example of a thiophenol mediated 8-*endo*-trig radical cyclization process has been reported.^{4a} In continuation of our studies on thiophenol mediated radical cyclization reactions for the synthesis of heterocycles,⁸ we report our preliminary results, on the thiophenol mediated 8-*endo* radical cyclizations toward the synthesis of oxocine-annulated heterocycles.

2. Results and discussions

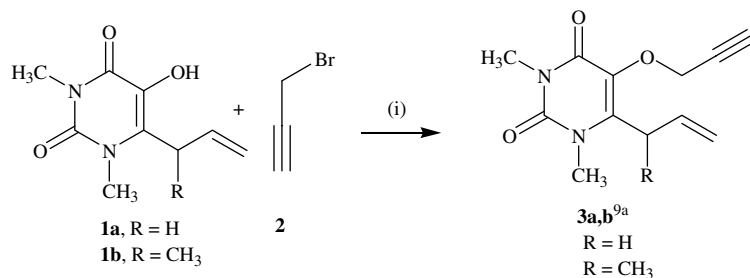
We chose substrates **3a–e** to investigate the generality of the sulfanyl radical addition–cyclization. The cyclization precursors **3a,b** were prepared by the reaction of compounds **1a,b** with propargyl bromide **2** according to an earlier published procedure^{9a} (Scheme 1). Similarly, other enyne derivatives **3c–e** were also prepared.^{9b–d}

The alkenyl radicals were generated by the addition of thiophenol to the terminal alkynes and their efficiency in tandem cyclization reactions were examined. Initially, substrate **3a** was investigated under different conditions.

Benzene, the most common solvent for radical reactions, was not the best choice for this radical cyclization process. The best results were obtained in refluxing *t*-butanol with slow addition of thiophenol (2 equiv) in the presence of the radical initiator AIBN. Interestingly,

Keywords: Thiophenol; Oxacycles; 8-*endo* Trig; Tandem cyclization.

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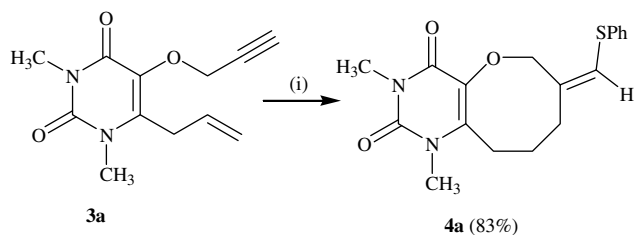
Scheme 1. Reagents and conditions: (i) dry acetone, anhyd K₂CO₃, reflux, 1.5–2 h.

the amount of the initiator played a crucial role in this process. The use of 2 equiv of AIBN with respect to the substrate proved to be the best compromise between the addition of thiophenol and cyclization, and the cyclized product **4a** was isolated as a crystalline solid in 83% yield (Scheme 2). A stoichiometric amount of AIBN with respect to the thiophenol was required for the reaction to go to completion indicating that the radical process was not efficient under the reaction conditions. Dimerization of thiyl radicals leading to diphenyl disulfide could explain this inefficiency. The use of a stoichiometric amount of AIBN allows regeneration of the thiyl radicals from either thiophenol or disulfide.¹⁰ Changing the solvent to higher boiling toluene did not improve the yield of the product. The structure of **4a** was confirmed by single crystal X-ray diffraction¹¹ (Fig. 1) and was characterized as 1,3-di-

methyl-7-[Z-1(phenylsulfanyl)methylidene]-2,3,4,6,7,8,9,10-octahydro-1*H*-oxocino[3,2-*d*]-pyrimidine.

Encouraged by this result, enynes **3b**, **3c**, and **3d** were treated in a similar manner to afford **4b**, **4c**, and **4d** in 82–85% yields. The results are summarized in Table 1. To synthesize a spirocyclic compound, we employed *C,C*-allyl-propargyl derivative **3e**^{9d} which was formed during the preparation of its isomer **3d**. Radical cyclization of **3e** under the above reaction conditions for 2.5 h afforded spirocarbocycle **4e** in 92% yield (Table 1).

The proposed mechanism of the thiophenol mediated reaction is depicted in Scheme 3. The phenyl thiyl radical, generated from thiophenol and AIBN, adds to the terminal alkyne to form vinyl radical **5**. This vinyl radical may undergo an 8-*endo* trig intramolecular cyclization with the adjacent alkene to form intermediate radical **6** which on abstraction of a H radical from thiophenol affords product **4**.



Scheme 2. Reagents and conditions: (i) dry *t*-butanol, PhSH, AIBN, reflux, 2 h.

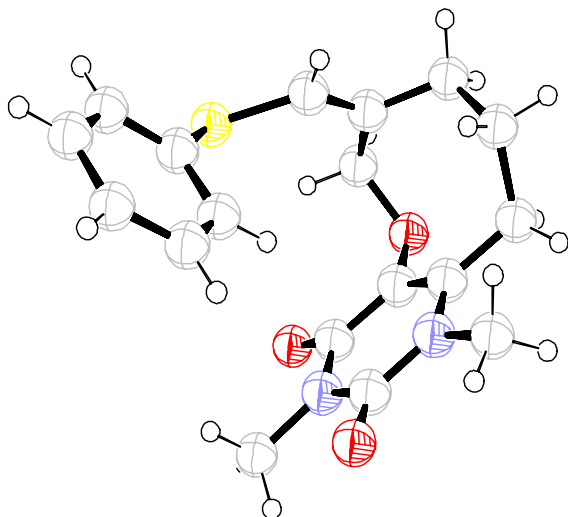
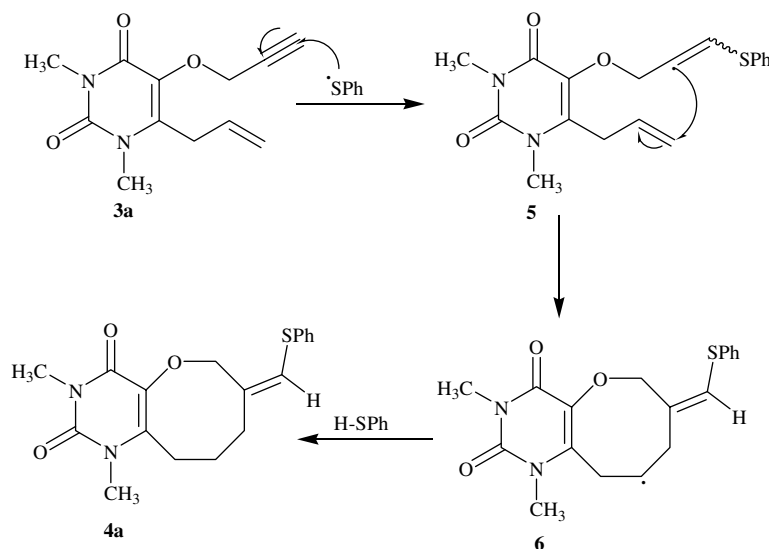


Figure 1. X-ray crystal structure of compound **4a**.

Table 1. Sulfanyl radical addition and cyclization of **3b–e**

Starting material 3	Product 4	Yield (%)
 3b ^{9a}	 4b	82
 3c ^{9b}	 4c	84
 3d ^{9c}	 4d	85
 3e ^{9d}	 4e	92



Scheme 3. Mechanism of the thiophenol-mediated cyclization.

In conclusion, we have developed a new efficient methodology for the synthesis of 8-membered ring ethers via sulfanyl radical addition–cyclization. Alkenyl radicals are generated from readily available terminal alkynes and thiophenol. The procedure presented here is more economic than other methods.^{1,5} The reaction was found to proceed under mild conditions. We believe that this procedure strongly enhances the synthetic potential of the addition–cyclization reaction developed by Naito. Application of this strategy for the synthesis of natural products is currently underway in our laboratory.

3. General procedure for the preparation of compounds 3a–e

Compounds 3a–e were synthesized according to the earlier published⁹ procedure.

Compounds 3a,b,^{9a} 3c,^{9b} 3d,^{9c} and 3e^{9d} were reported earlier.

3.1. Typical experimental procedure for radical cyclization of compounds 3a–e

A deoxygenated solution of thiophenol (2 equiv) in dry *t*-butanol was added dropwise to a solution of the radical precursor 3a (0.29 mmol, 100 mg) in refluxing anhydrous *t*-butanol under a nitrogen atmosphere. The radical initiator AIBN (0.29 mmol, 50 mg) was added and the mixture was refluxed until complete disappearance of the starting material (TLC). The solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (10 mL) and stirred with saturated NaHCO₃ solution (10 mL) for 2 h. The aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL) and the combined CH₂Cl₂ extracts were washed with water (2 × 20 mL), brine solution (1 × 20 mL), and dried (Na₂SO₄). The solvent was evaporated under reduced pressure. The crude product was purified by silica gel

column chromatography using gradient elution with ethyl acetate:petroleum ether (1:4) to afford the crystalline solid 4a.

3.2. Compound 4a

Yield: 83%; solid; mp: 110–111 °C; IR (KBr): $\nu = 2916, 1715, 1618 \text{ cm}^{-1}$; ¹H NMR (CDCl₃, 500 MHz): $\delta_{\text{H}} = 1.86\text{--}1.98$ (m, 2H), 2.45–2.48 (m, 2H), 2.82–2.84 (m, 2H), 3.21 (s, 3H), 3.45 (s, 3H), 4.83 (s, 2H), 5.10 (s, 1H), 7.08 (d, $J = 7.4 \text{ Hz}$, 1H), 7.17–7.29 (m, 4H) ppm; ¹³C NMR (100 MHz): 26.3, 28.3, 29.2, 30.8, 31.8, 67.4, 118.8, 120.1, 127.0, 129.0, 130.4, 131.1, 134.7, 143.4, 151.3, 155.6 ppm; MS: $m/z = 344$ (M⁺). Anal. Calcd for C₁₈H₂₀N₂O₃S: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.86; H, 5.89; N, 8.19.

3.3. Compound 4b

Yield: 82%; solid; mp: 102–104 °C; IR (KBr): $\nu = 2923, 1717, 1634 \text{ cm}^{-1}$; ¹H NMR (CDCl₃, 400 MHz): $\delta_{\text{H}} = 0.78$ (d, $J = 7.0 \text{ Hz}$, 3H), 1.62–1.68 (m, 2H), 1.90–1.95 (m, 1H), 2.16–2.21 (m, 1H), 2.31–2.36 (m, 1H), 2.49 (s, 3H), 3.28 (s, 3H), 3.41 (d, $J = 14.2 \text{ Hz}$, 1H), 3.63 (d, $J = 14.2 \text{ Hz}$, 1H), 5.08 (s, 1H), 7.15–7.22 (m, 2H), 7.27–7.34 (m, 3H) ppm; ¹³C NMR (100 MHz): 14.8, 25.1, 29.1, 29.6, 32.6, 35.4, 68.0, 117.6, 119.7, 127.1, 129.0, 130.1, 131.5, 136.0, 144.6, 151.2, 157.0 ppm; MS: $m/z = 358$ (M⁺). Anal. Calcd for C₁₉H₂₂N₂O₃S: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.85; H, 6.30; N, 7.87.

3.4. Compound 4c

Yield: 84%; solid; mp: 88–90 °C; IR (KBr): $\nu = 2922, 1735, 1681 \text{ cm}^{-1}$; ¹H NMR (CDCl₃, 500 MHz): $\delta_{\text{H}} = 1.49\text{--}1.64$ (m, 2H), 1.74–1.79 (m, 1H), 1.86–1.91 (m, 1H), 2.04–2.10 (m, 1H), 2.43–2.49 (m, 1H), 3.46 (s, 3H), 3.50 (d, $J = 13.8 \text{ Hz}$, 1H), 3.86 (d, $J = 13.8 \text{ Hz}$, 1H), 5.48 (s, 1H), 6.45 (dd, $J = 1.3, 7.6 \text{ Hz}$, 1H), 6.87 (t, $J = 7.5 \text{ Hz}$, 1H), 7.01 (d, $J = 7.4 \text{ Hz}$, 1H), 7.26–7.35

(m, 4H), 7.45 (d, $J = 7.1$ Hz, 2H) ppm; ^{13}C NMR (125 MHz): 18.4, 26.9, 30.4, 33.0, 42.6, 54.8, 115.7, 122.2, 124.5, 127.2, 128.90, 128.94, 129.1, 129.4, 131.6, 135.8, 137.1, 140.4, 157.5, 194.4 ppm; HRMS: m/z calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_2\text{SNa}$ $[\text{M}+\text{Na}]^+$: 386.1172; found: 386.1191.

3.5. Compound 4d

Yield: 85%; solid; mp: 166–168 °C; IR (KBr): $\nu = 2921$, 1713, 1678 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): $\delta_{\text{H}} = 1.86$ – 2.02 (m, 2H), 2.23 (t, $J = 5.6$ Hz, 4H), 3.48 (d, $J = 4.6$ Hz, 2H), 5.43 (s, 1H), 7.06–7.12 (m, 2H), 7.17–7.24 (m, 3H), 7.30–7.36 (m, 2H), 7.43–7.52 (m, 4H), 8.16 (dd, $J = 1.9$, 7.6 Hz, 1H), 8.40 (dd, $J = 1.9$, 4.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz): 19.0, 29.0, 42.3, 60.4, 112.7, 119.2, 124.9, 125.8, 126.6, 127.0, 128.0, 128.4, 128.7, 128.8, 129.4, 129.5, 135.0, 141.0, 149.8, 150.5, 153.9, 172.2 ppm; MS: $m/z = 426$ (M^+). Anal. Calcd for $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: C, 73.21; H, 5.20; N, 6.57. Found: C, 73.37; H, 5.16; N, 6.65.

3.6. Compound 4e

Yield: 92%; solid; mp: 154–156 °C; IR (KBr): $\nu = 2927$, 1709, 1657 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): $\delta_{\text{H}} = 1.20$ – 1.30 (m, 4H), 2.00–2.13 (m, 1H), 2.51–2.57 (m, 1H), 3.06–3.12 (m, 1H), 3.30–3.41 (m, 1H), 5.99 (t, $J = 2.2$ Hz, 1H), 7.09–7.13 (m, 1H), 7.15–7.24 (m, 3H), 7.27–7.38 (m, 4H), 7.45–7.52 (m, 3H), 8.27 (d, $J = 6.3$ Hz, 1H), 8.43 (d, $J = 3.9$ Hz, 1H) ppm; ^{13}C NMR (100 MHz): 29.6, 38.8, 39.2, 44.2, 63.2, 113.0, 119.0, 125.8, 125.9, 127.0, 128.7, 128.8, 128.9, 129.5, 132.2, 136.7, 136.8, 136.9, 149.8, 154.3, 173.7, 194.5 ppm; MS: $m/z = 426$ (M^+). Anal. Calcd for $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: C, 73.21; H, 5.20; N, 6.57. Found: C, 73.44; H, 5.33; N, 6.62.

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References and notes

- For a review, see: (a) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631; (b) Yamaguchi, S.; Tsuchida, N.; Miyazawa, M.; Hirai, Y. *J. Org. Chem.* **2005**, *70*, 7505; (c) Lang, S.; Corr, M.; Muir, N.; Khan, T. A.; Schonebeck, F.; Murphy, J. A.; Payne, A. H.; Williams, A. C. *Tetrahedron Lett.* **2005**, *46*, 4027; (d) Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V. *Chem. Commun.* **2002**, 634; (e) Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Panda, J.; Ghosh, S. *J. Org. Chem.* **2000**, *65*, 482; (f) Dzwiniel, T. L.; Stryker, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9184; (g) Shanmugam, P.; Rajasingh, P. *Tetrahedron Lett.* **2005**, *46*, 3369; (h) Pirrung, F. O. H.; Hiemstra, H.; Speckamp, W. N.;

Kaptein, B.; Schoemaker, H. E. *Tetrahedron* **1994**, *50*, 12415, and references cited therein.

- (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: New York, 1986; (b) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1; (c) Malacria, M. *Chem. Rev.* **1996**, *96*, 289; (d) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237; (e) Majumdar, K. C.; Basu, P. K. *Heterocycles* **2002**, *57*, 2413; (f) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2004**, *60*, 6239; (g) Majumdar, K. C.; Alam, S. *Org. Lett.* **2006**, *8*, 4059.
- (a) Cid, M. M.; Dominguez, D.; Castedo, L.; Vazquez-Lopez, E. M. *Tetrahedron* **1999**, *55*, 5599; (b) Magono, H.; Hara, S. *Tetrahedron Lett.* **2004**, *45*, 4329; (c) Rodriguez, G.; Cid, M. M.; Saa, C.; Castedo, L.; Dominguez, D. *J. Org. Chem.* **1996**, *61*, 2780; (d) Wu, S.; Journet, M.; Malacria, M. *Tetrahedron* **1994**, *35*, 8601; (e) Fidalgo, J.; Castedo, L.; Dominguez, D. *Tetrahedron* **1993**, *34*, 7317.
- (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612; (b) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Chem. Commun.* **1997**, *1*, 637; (c) Blake, A. J.; Hollingworth, G. J.; Pattenden, G. *Synlett* **1996**, 643; (d) Nandi, A.; Chattopadhyay, P. *Tetrahedron Lett.* **2002**, *43*, 5977.
- Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2006**, *47*, 1599.
- (a) Miyata, O.; Muroya, K.; Kobayashi, Y.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459; (b) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199; (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**, *iii*, 220; (e) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 19; (f) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.; Naito, T. *J. Org. Chem.* **2002**, *65*, 6922; (g) Miyata, O.; Nakajima, E.; Naito, T. *Chem. Pharm. Bull.* **2001**, *49*, 213.
- (a) Miyata, O.; Naito, T. *C.R. Acad. Sci. Paris, Chim.* **2001**, *4*, 401; (b) Lachia, M.; Denes, F.; Beaufls, F.; Renaud, P. *Org. Lett.* **2005**, *7*, 4103; (c) Harrowven, D. C.; Maj, P. J.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 503; (d) Fernandez, M.; Alonso, R. *Org. Lett.* **2005**, *7*, 11; (e) Martinez-Grau, A.; Curran, D. P. *Tetrahedron Lett.* **1997**, *53*, 5679; (f) Burke, S. D.; Jung, K. W. *Tetrahedron Lett.* **1994**, *35*, 5837; (g) Beaufls, F.; Denes, F.; Renaud, P. *Org. Lett.* **2004**, *6*, 2563; (h) Capella, L.; Montevcehi, P. C.; Navacehia, M. L. *J. Org. Chem.* **1996**, *61*, 6783; (i) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. *Org. Lett.* **2003**, *5*, 1313; (j) Carta, P.; Puljic, N.; Robert, C.; Dhimane, A. L.; Fensterbank, L.; Lacote, E.; Malacria, M. *Org. Lett.* **2007**, *6*, 1061.
- (a) Majumdar, K. C.; Debnath, P.; Maji, P. K. *Tetrahedron Lett.* **2007**, *48*, 5265; (b) Majumdar, K. C.; Debnath, P.; Alam, S.; Maji, P. K. *Tetrahedron Lett.* **2007**, *48*, 7031.
- (a) Majumdar, K. C.; Maji, P. K.; Rahaman, H.; Roy, B. *Let. Org. Chem.* **2006**, *3*, 845; (b) Majumdar, K. C.; Debnath, P.; Samanta, S. *Let. Org. Chem.* **2007**, *4*, 309; (c) Majumdar, K. C.; Rahaman, H.; Islam, R.; Roy, B. *Tetrahedron Lett.* **2006**, *47*, 2111; (d) Majumdar, K. C.; Islam, R.; Rahaman, R.; Roy, B. *Org. Biomol. Chem.* **2006**, *4*, 2393.
- Beaufls, F.; Denes, F.; Becattini, B.; Renaud, P. *Adv. Synth. Catal.* **2005**, *347*, 1587.
- CCDC reference no. for the CIF file of compound **4a**: CCDC-658345.