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An easy access to pyrimidine-fused azocine derivatives by thiophenol-mediated radical cyclization via 8-*endo*-trig mode

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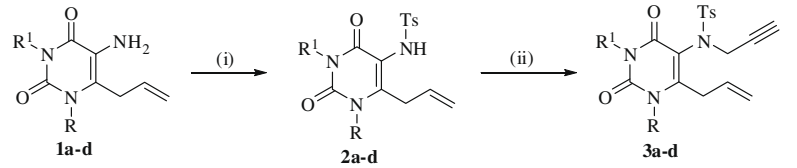
ABSTRACT

An efficient route for the synthesis of eight-membered nitrogen heterocycles has been developed via a thiophenol-mediated intramolecular 8-*endo*-trig radical cyclization. The radical precursors were prepared using $BF_3{\cdot}Et_2O$-catalyzed aza-Claisen rearrangement followed by the reaction with propargyl bromide. The alkenyl radicals are generated from thiophenol initiated by the benzoyl peroxide instead of commonly used AIBN for easy and facile isolation of the pure products.

Medium-sized N-containing fused ring systems, in particular eight-membered rings (azocine) are core structures of various structurally remarkable natural products.[1–3] They constitute an important class of compounds which are used as precursors in the synthesis of biologically active compounds. Annulated azocines have recently been demonstrated to possess substantial bioactivity as preventives of urinary disturbances,[4] AChE inhibitors,[5] and 17-β-hydroxysteroid dehydrogenase inhibitors.[6] As the direct formation of this ring system from acyclic precursors is entropically and enthalpically not favoured, an efficient construction of this ring is a challenging problem.

There are several classical cyclization approaches available for synthesizing azocine, for example, cycloaddition,[7] fragmentation reaction,[8] Dieckmann cyclization,[9] tandem hydroboration reaction,[10] and Michael reaction.[11] Recently, Pd-catalyzed intramolecular cyclization has also been applied for the synthesis of azocine derivatives.[12] However, any radical-mediated cyclization method has not been so far explored in their preparation. In continuation of our work on radical chemistry and the synthesis of biologically active heterocycles,[13] we have recently reported[14] an efficient synthesis of 9-deazaxanthines. This success has prompted us to undertake a study on the use of benzoyl peroxide in the thiophenol-mediated 8-*endo*-trig radical cyclization for the synthesis of pyrimidine-annulated azocine derivatives. Herein, we report our results.

The required precursors **3**(**a**–**d**) for the synthesis of pyrimidine-fused azocine derivatives by the thiophenol-mediated radical cyclization were prepared in 90–93% yields by the reaction of **2**(**a**–**d**) with propargyl bromide in the presence of anhydrous K_2CO_3 in refluxing acetone for 4–5 h. The compounds **2(a–d)** were in turn



1a-d
a, R = R^1 = Me
b, R = R^1 = Et
c, R = Et, R^1 = Me
d, R = Et, R^1 = H

2a-d
a, R = R^1 = Me, 90%
b, R = R^1 = Et, 97%
c, R = Et, R^1 = Me, 95%
d, R = Et, R^1 = H, 98%

3a-d
a, R = R^1 = Me, 92%
b, R = R^1 = Et, 91%
c, R = Et, R^1 = Me, 93%
d, R = Et, R^1 = H, 90%

Scheme 1. Synthesis of precursors **3a–d.** Reagent and conditions: (i) TsCl, Py, 80 °C, 1-2 h; and (ii) propargyl bromide, K_2CO_3, acetone, reflux, 4–5 h.

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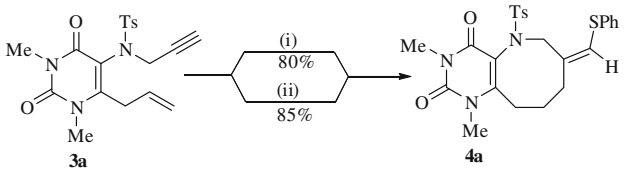


Scheme 2. Synthesis of azocine derivative **4a**. Reagent and conditions: (i) dry *t*-butanol, PhSH, AIBN, reflux, 2 h; and (ii) dry *t*-butanol, PhSH, benzoyl peroxide, reflux, 2 h.

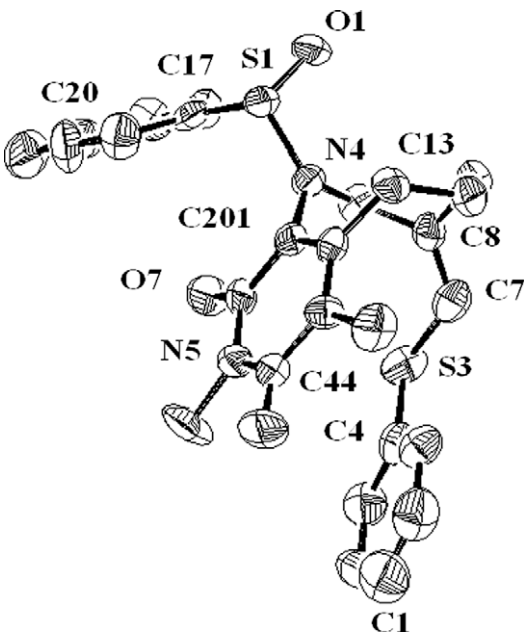
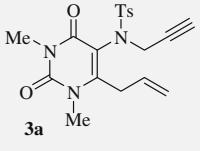
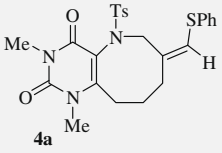
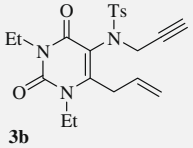
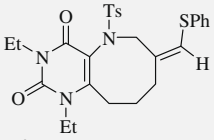
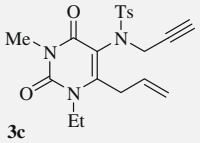
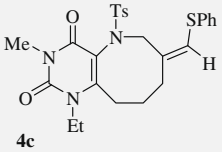
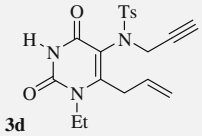
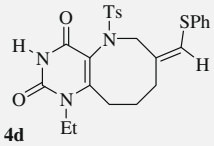


Figure 1. Ortep diagram of compound **4a**.

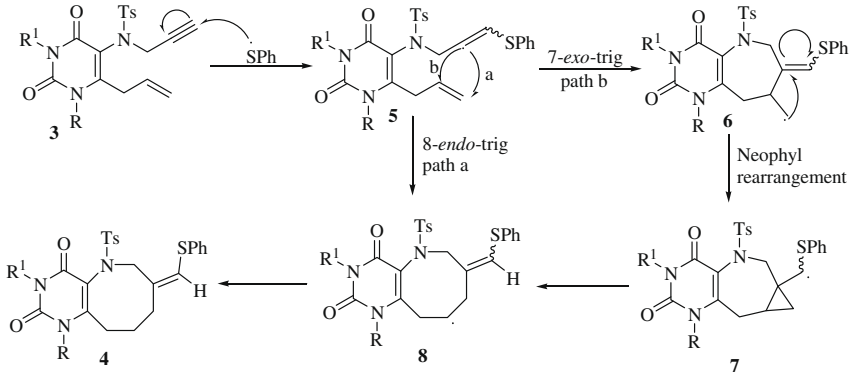
prepared in excellent yields (90–98%) by tosylation of **1**(**a**–**d**) using *p*-TsCl and pyridine at 80 °C for 1–2 h. Compounds **1(a–d)** were accessed following published procedure.[14,15] The synthetic route for the preparation of precursors **3**(**a**–**d**) is depicted in Scheme 1.

We next turned our attention to the synthesis of azocine derivatives. For this purpose, the alkenyl radicals were generated by the addition of thiophenol to the terminal alkynes. We then examined their efficiency in tandem cyclization. Initially, substrate **3a** was investigated under different conditions. The reaction was conducted in refluxing *t*-butanol with slow addition of thiophenol (2 equiv) in the presence of the radical initiator AIBN (azobisisobutyronitrile). Interestingly, the amount of the initiator played a crucial role in this reaction. The use of 2 equiv of AIBN with respect to the substrate proved to be the best compromise between the addition of thiophenol and the cyclization. The cyclized product **4a** was isolated as a white solid in 80% yield. However, the use of higher AIBN excess caused the difficulty during the separation of the product **4a** from an appreciable amount of starting initiator. To avoid this problem, we have used 2 equiv of benzoyl peroxide as initiator in place of AIBN. The reaction was complete within 2 h to afford 85% yield of **4a**[16] (Scheme 2). In contrast, a stoichiometric amount of radical initiator with respect to thiophenol indicated that the radical process was not efficient. Dimerization of thiyl radicals leading to diphenyl disulfide could explain this inefficiency. The use of a stoichiometric amount of radical initiator allows regeneration of the thiyl radicals from either the thiophenol or disulfide.[17]

Table 1
Synthesis of pyrimidine containing azocine derivatives **4a–d**

Entry	Azocine precursor **3**	Azocine derivative**4**	Yield (%)
1	 **3a**	 **4a**	85
2	 **3b**	 **4b**	82
3	 **3c**	 **4c**	83
4	 **3d**	 **4d**	70

The product of **4a** was characterized from its spectral data and the *cis*-(*Z*)-configuration of the exocyclic double bond was settled by single crystal X-ray diffraction[18] (Fig. 1).



Scheme 3. Proposed reaction pathway for thiophenol-mediated radical cyclization reaction for synthesizing azocine derivatives.

Encouraged by this result, other enynes **3**(**b**–**d**) were similarly treated to afford **4**(**b**–**d**) in 70–83% yields. The results are summarized in Table 1.

The phenylsulfanyl radical, generated from thiophenol and benzoyl peroxide, adds to the terminal alkynes of enynes **3** to form vinyl radicals **5**. These vinyl radicals may undergo an 8-*endo*-trig intramolecular cyclization with the adjacent alkene to form the hypothetical intermediate **8** which may afford product **4** by abstraction of a H radical from thiophenol. An alternative pathway (path b), a 7-*exo*-trig cyclization followed by 1,2-alkenyl migration via a cyclopropyl methyl radical **7** (neophyl rearrangement)[19] would also lead to the same product **4**. This may be an indication that the reaction proceeds via a ring expansion process (Scheme 3, path b), that is ring opening of the cyclopropylmethyl radical intermediate may be stereoselective. The proposed mechanism of the thiophenol-mediated reaction is depicted in Scheme 3.

In conclusion, we have developed a new efficient methodology for the synthesis of azocine derivatives via sulfanyl radical addition–cyclization reaction. To the best of our knowledge, this is the first example for the synthesis of azocine derivatives by thiophenol-mediated radical cyclization. The use of benzoyl peroxide in the place of usual radical initiator AIBN offers easy and facile separation of the pure products. Application of this strategy to the synthesis of other bioactive azocine derivatives is under way, and a full account will be communicated in due course.

Acknowledgments

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16. *General procedure for the synthesis of azocine derivatives* **4**(**a**–**d**) *by thiophenol-mediated radical cyclization*: A deoxygenated solution of thiophenol (0.40 mmol, 0.04 mL) in dry *t*-butanol (3 mL) was added dropwise to a solution of compound **3a** (0.20 mmol, 100 mg) in refluxing anhydrous *t*-butanol (3 mL) under a nitrogen atmosphere. The radical initiator benzoyl peroxide (0.40 mmol, 97 mg) was added and refluxed for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and stirred with saturated $NaHCO_3$ solution (10 mL) for 2 h. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL), and the combined organic extracts were washed with water (2×15 mL), brine solution, (10 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using 10% EtOAc/Pet. ether as eluent to afford the azocine derivative **4a** (109 mg, 85%) as a white solid. The other substrates **3**(**b**–**d**) were similarly treated to give products **4**(**b**–**d**).
(Z)-1,3-Dimethyl-7-(phenylthiomethylene)-5-tosyl-5,6,7,8,9,10- hexahydropyrimido-[5,4-b]azocine-2,4(1H,3H)-dione (**4a**): White solid, mp 222–224 °C, yield 85%. IR (KBr, cm^{-1}) ν_{max}: 2927, 1707, 1655; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.23–2.27 (m, 1H), 2.42 (s, 3H), 2.47–2.50 (m, 1H), 2.58–2.61 (m, 1H), 2.68–2.73 (m, 1H), 3.01 (s, 3H), 3.41–3.48 (m, 2H), 3.50 (s, 3H), 4.24 (d, 1H, J = 13.4 Hz), 4.36 (d, 1H, J = 13.4 Hz), 6.18 (s, 1H), 6.96 (d, 2H, J = 7.5 Hz), 7.14 (t, 1H, J = 7.1 Hz), 7.18 (t, 2H, J = 7.0 Hz), 7.30 (d, 2H, J = 7.9 Hz), 7.83 (d, 2H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 28.2, 28.8, 29.4, 32.4, 35.3, 51.7, 111.3, 125.5, 126.2, 127.7, 128.3, 129.0, 129.4, 136.1, 136.7, 140.6, 143.7, 151.7, 159.1, 159.7; MS (*m/z*): 497 [M^+]. Anal. Calcd for $C_{25}H_{27}N_3O_4S_2$: C, 60.34; H, 5.47; N, 8.44. Found: C, 60.47; H, 5.51; N, 8.40.
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