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Thiophenol-mediated intramolecular radical cyclization: an efficient method for the synthesis of benzoxocine derivatives

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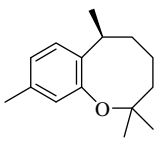
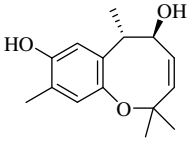
ABSTRACT

A new, efficient, high yielding method for the synthesis of benzoxocine derivatives has been developed via a thiophenol-mediated intramolecular 8-*endo* radical cyclization. This method allowed the synthesis of the backbone of several sesquiterpenes.

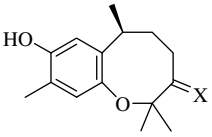
The search for new methods for the construction of organic molecules from simple starting materials is an ongoing challenge for organic chemists. The synthesis of medium and large ring ethers, especially those annulated with aromatic rings such as benzoxepines and benzooxocines, is of current interest due to their presence in a large number of bioactive natural products.[1] Some examples of natural products containing the 3,4,5,6-tetrahydro-2*H*-benzo[*b*]oxocine core structure include helianane,[2] heliannuols A and K,[3,4] and protosappanine B.[5] Sevaral 5,6-dihydro-2*H*-benzo[*b*]oxocines are found in heliannuols G and H,[2] specionine and sophoroside A.[6] The characteristic phytotoxic activity and the unique structural features enshrined in these compounds have made them attractive targets for synthesis.[7]



Helianane



Heliannuol H



Heliannuol A, X = H, OH
Heliannuol K, X = O

Snieckus reported the synthesis of benzene-fused oxygen heterocycles by combination of directed-*ortho*-metalation and ring closing metathesis (RCM).[8] A number of benzo[*b*]oxepin and benzo[*b*]oxocine natural products were also prepared based on RCM.[9] Langer et al. reported the synthesis of 2,5-benzoxepins and 5,6-dihydro-2*H*-benzo[*b*]oxocines by the combination of [3+3] cyclizations and RCM.[10] However, general cost effective methods for the synthesis of these ring systems under mild reaction conditions are scarce.

Intramolecular radical cyclization reactions have been developed for carbon–carbon bond formation, and represent a powerful tool in modern synthetic chemistry.[11] Although tin hydride mediated radical reactions have been used for the synthesis of medium-sized oxacycles,[12] there are many drawbacks[13] associated with such tin-based radical reactions. It is therefore not surprising that many groups have started research programs directed towards tin-free radical chemistry.[14,15] Recently, Naito et al.[16] explored a new, efficient, tin-free carbon–carbon bond forming process based on sulfanyl radical[17,18] addition and cyclization. In our earlier study,[19] we reported a novel, high yielding protocol for the construction of medium-sized cyclic ethers by thiophenol-mediated tandem radical addition–cyclizations of various enyne systems. The success of this methodology prompted us to undertake a further study on thiophenol-mediated radical cyclizations towards the synthesis of benzoxocine derivatives which would provide a procedure for the construction of the benzoxocine skeleton present as a basic structural moiety in a number of natural sesquiterpenes.

The radical precursors **2a**–**g** required for the present investigation were synthesized in 88–96% yields by refluxing 2-allyl phenols with propargyl bromide in dry acetone in the presence of anhydrous K_2CO_3 (Scheme 1). The 2-allyl phenols were in turn prepared by Claisen rearrangement of the corresponding allylphenyl ethers.

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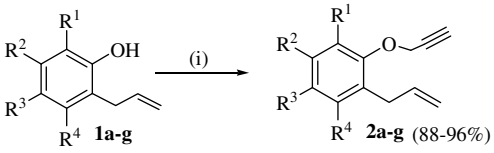


2a. $R^1 = R^4 = H$, $R^2 = CH_3$, $R^3 = Cl$
2b. $R^1 = R^3 = H$, $R^2 = R^4 = CH_3$
2c. $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$
2d. $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$
2e. $R^1 = R^3 = CH_3$, $R^2 = R^4 = H$
2g. $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$
2f. $R^1 = R^2 = R^3 = H$, $R^4 = Cl$

Scheme 1. Synthesis of starting materials. Reagents and conditions: (i) propargyl bromide, dry acetone, K_2CO_3, reflux, 4–6 h.

The alkenyl radicals were generated by the addition of phenylsulfanyl radicals to the terminal alkynes and their efficiency in tandem cyclizations were examined. Initially, substrate **2a** was studied under different conditions.

A diastereomeric mixture of the corresponding vinyl sulfanylphenyl adduct was formed in 82%, when a 0.1 M solution of **2a**, PhSH (atmosphere, 2 equiv) and AIBN (2 equiv) was refluxed in dry *t*-butanol for 4 h under a nitrogen atmosphere however, no cyclization product was detected. The failure of cyclization led us to consider changing the solvent. After surveying the reaction conditions using **2a** as precursor, we found that using 0.01 M benzene solution was effective for the radical cyclization which gave as 82% of cyclized product **3a**[20] (Scheme 2). Under these reaction conditions, formation of the reduced vinyl adduct was not observed.

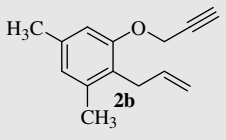
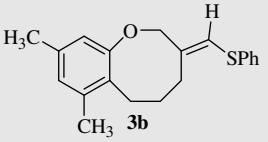
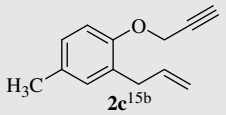
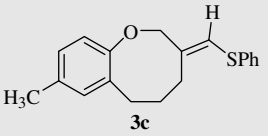
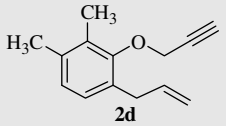
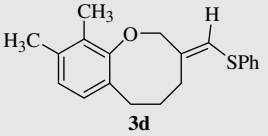
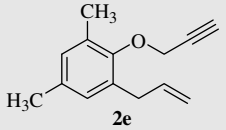
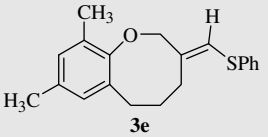
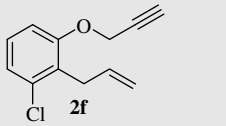
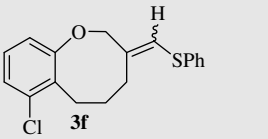
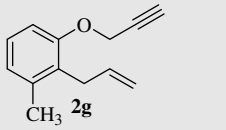
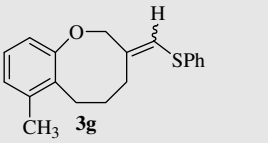
Interestingly, the amount of initiator played a crucial role in this process. The use of 2 equiv of AIBN was required for completion of the reaction and to obtain the high yields of the cyclized products. With 1 equiv of AIBN, the reactions were extremely slow and gave lower yields of the cyclization product (37%); with 0.5 equiv of AIBN, no reaction occurred. Dimerization of thiyl radicals leading to diphenyl disulfide could explain this inefficiency. The use of a stoichiometric amount of AIBN allows regeneration of the phenylsulfanyl radicals from either thiophenol or disulfide. Changing the solvent to the higher boiling toluene did not improve the yield of product further.

The stereochemistry of the exocyclic double bond in **3a** was found to be exclusively *E* on the basis of an NOE correlation between the methylene ($-OCH_2$) resonance at $\delta = 4.46$ ppm and the exocyclic proton at $\delta = 5.90$ ppm. The stereochemical outcome of the reaction is difficult to understand. Naito et al. obtained a mixture of isomers and the main stereoisomer was the one in which the SPh group and the new C–C bond were *anti* to each other. In our earlier work,[19] we obtained exclusively the *Z*-isomer where the SPh group and newly formed C–C bond were *anti* to each other. The reason for the *E*-selectivity is not clear at present.

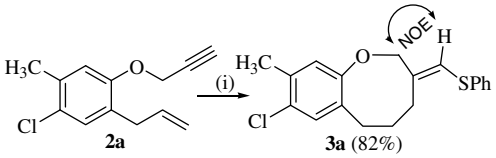
In order to examine the versatility of this intramolecular addition–cyclization reaction, enynes **2b–g** were reacted under the optimized conditions and after column chromatography, afforded benzoxocines **3b–g** in 72–85% yields. The results are summarized in Table 1. When the substrates **2a–e** were treated with AIBN and PhSH in refluxing benzene, cyclization proceeded with 100% diastereoselectivity. However, reaction of substrates **2f** and **2g** having an *ortho* substituent with respect to the allyl group, under similar conditions, resulted in a diastereomeric mixture of cyclized products **3f** and **3g** in 72% and 78% yields, respectively. The products were isolated as diastereomeric mixtures in the ratios 3:2, which were not separable by column chromatography.

The 8-*endo* radical cyclization was further extended for the synthesis of naphthyl annulated oxocine derivative **3h**. Here, it is important to note that under the above optimized conditions, substrate **2h**[15b] gave the cyclized product **3h** in 55% yield along with recovered starting material (35%). However, when the reac-

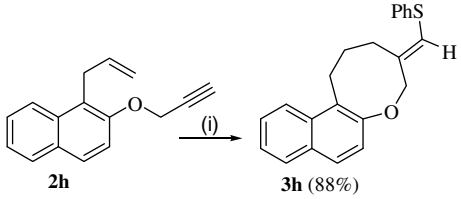
Table 1
Thiophenol-mediated radical cyclizations of **2b–g** to **3b–g**[a]

Entry	Starting material **2**	Product **3**	Yield (%)
1	 **2b**	 **3b**	76
2	 **2c**[15b]	 **3c**	85
3	 **2d**	 **3d**	82
4	 **2e**	 **3e**	80
5	 **2f**	 **3f**	72 (3:2)[b]
6	 **2g**	 **3g**	78 (3:2)[b]

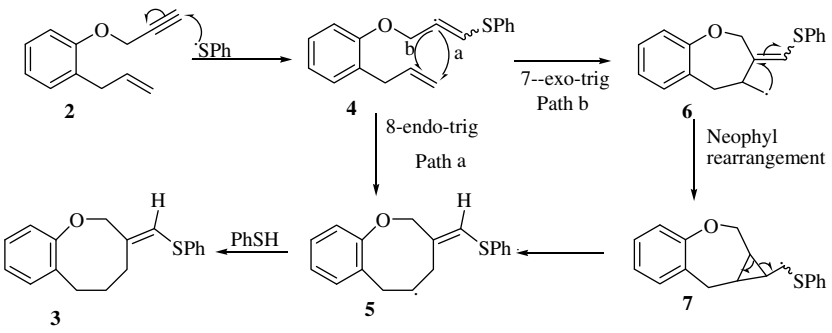
[a] Isolated yield.
[b] Diastereometric ratio determined from the ^1H NMR spectrum.



Scheme 2. Thiophenol-mediated radical cyclization. Reagents and conditions: (i) PhSH (2 equiv), AIBN (2 equiv), benzene, reflux.



Scheme 3. Sulfanyl radical cyclization onto a naphthalene moiety. Reagents and conditions: (i) PhSH (2 equiv), AIBN (2 equiv), toluene, reflux.



Scheme 4. Mechanism of the sulfanyl radical addition–cyclization reaction.

tion was carried out in refluxing toluene with PhSH (2 equiv) and AIBN (2 equiv), the 8-*endo* cyclized product was obtained in 88% yield (Scheme 3).

The proposed mechanism of the thiophenol-mediated reaction is depicted in Scheme 4. The phenylsulfanyl radical, generated from thiophenol and AIBN, adds to the terminal alkyne of enyne **2** to form vinyl radical **4**. The high *E*-selectivity of double bond formation may be explained by the trapping of the intermediary vinyl radical **4** (via as 8-*endo*-trig mode, path a) from the opposite face, followed by hydride radical transfer from thiophenol to the radical intermediate **5** to afford product **3**. An alternative pathway (path b), a 7-*exo* cyclization process followed by 1,2-alkenyl migration via a cyclopropyl methyl radical **7** (neophyl rearrangement) would also lead to the same product **3**. This may be an indication that the reaction is proceeds via a ring expansion process (Scheme 4, path b), that is ring opening of the cyclopropylmethyl radical intermediate may be stereoselective.

In conclusion, we have developed a new and efficient method for the synthesis of benzoxocine derivatives 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 for the synthesis of benzoxocine derivatives. Moreover, during the cyclization process, a phenylthio moiety is incorporated into the final products. This functionalization is particularly attractive for further transformation of the products.[21] The application of this strategy for the synthesis of benzoxepine and benzoxocine related natural products is currently underway in our laboratory.

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20. All new compounds reported here gave satisfactory spectroscopic and/or analytical data. Data for compound **3a**: Yield: 82%; solid; mp: 88–90 °C (petroleum ether); IR (KBr): ν = 2937, 1582, 1457, 1255, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.76–1.81 (m, 2H), 2.32 (s, 3H), 2.44 (t, J = 6.1 Hz, 2H), 2.83 (t, J = 5.9 Hz, 2H), 4.46 (s, 2H), 5.90 (s, 1H), 6.82 (d, J = 8.5 Hz, 1H),

6.96–6.98 (m, 2H), 7.14–7.17 (m, 1H), 7.18 (d, J = 8.5 Hz, 1H), 7.21–7.25 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): 16.7, 26.4, 27.4, 32.2, 82.3, 120.4, 125.5, 126.8, 128.1, 129.1, 129.4, 130.7, 135.2, 136.2, 137.8, 140.5, 156.0 ppm. HRMS: m/z calcd for $C_{19}H_{19}ClOSNa$ $[M+Na]^+$: 353.0743; found: 353.0742.

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