Present work on the thiol-mediated 8-endo-trig radical cyclization: an easy access to medium-sized cyclic ethers

Discussion
Several methods\textsuperscript{108} 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.\textsuperscript{70a,109} Much attention has been paid to the construction of five- and six-membered rings by radical cyclization.\textsuperscript{70a,109} However, there are problems associated with 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-\textit{endo}-trig cyclization strategy.\textsuperscript{110} There are few examples in the literature for the construction of eight-membered ring systems by radical cyclization.\textsuperscript{111} Recently, Roy \textit{et al.}\textsuperscript{112} described titanocene(III) mediated 8-\textit{endo} radical cyclization for the synthesis of eight-membered cyclic ethers. Naito \textit{et al.}\textsuperscript{85,86,87b,97,113} have explored a new, efficient carbon-carbon bond forming reaction based on sulfanyl radical addition and cyclization. These radical reactions proceed \textit{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. Thiophenol\textsuperscript{76,114} is a very efficient 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.\textsuperscript{113a,114a} To the best of our knowledge, only one example of a thiophenol mediated 8-\textit{endo}-trig radical cyclization process has been reported.\textsuperscript{99} In continuation of our studies on thiophenol mediated radical cyclization reactions for the synthesis of heterocycles,\textsuperscript{80,106} we report our preliminary results, on the thiophenol mediated 8-\textit{endo} radical cyclizations towards the synthesis of oxocine-annulated heterocycles. Here we report our.

We chose substrates 278a-e to investigate the generality of the sulfanyl radical addition-cyclization. The cyclization precursors 278a,b were prepared by the reaction of compounds 276a,b with propargyl bromide according to the earlier published procedure\textsuperscript{115a} (Scheme 62). Similarly, other enyne derivatives 278c-e were also prepared.\textsuperscript{115b-d}
The alkenyl radicals were generated by addition of thiophenol to the terminal alkynes and their efficiency in tandem cyclization reactions were examined. Initially, substrate 278a 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, the amount of the initiator played a crucial role in this process. The use of two equivalents of AIBN with respect to the substrate proved to be the best compromise between the addition of thiophenol and cyclization, and the cyclized product 279a was isolated as a crystalline solid in 83% yield (Scheme 63). A stoichiometric amount of AIBN with respect to the thiophenol is 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 by either thiophenol or disulfide.116 Changing
the solvent to higher boiling toluene did not improve the yield of the product. The structure of 279a was confirmed by single crystal X-ray diffraction (Fig. 4) and was characterized as 1,3-dimethyl-7-[Z-1-(phenylsulfanyl)methylidene]-2,3,4,6,7,8,9,10-octahydro-1H-oxocino[3,2-d]pyrimidine.

![Figure 4. X-ray crystal structure of compound 279a](image)

Encouraged by this result, the enynes 278b, 278c and 278d were treated in a similar manner to afford 279b, 279c and 279d in 82-85% yields. The results are summarized in Table 12. In order to synthesize a spirocyclic compound, we employed C,C-allyl-propargyl derivative 278e which was formed during the preparation of its isomer 278d. Radical cyclization of 278e under the above reaction conditions for 2.5 h afforded the spirocarbicycle 278e in 92% yield (Table 12).

The proposed mechanism of the thiophenol-mediated reaction is depicted in Scheme 64. The phenyl thiyl radical, generated from thiophenol and AIBN, adds to the terminal alkyne to form vinyl radical 280. This vinyl radical may undergo an 8-endo trig intramolecular cyclization with the adjacent alkene to form intermediate radical 281 which on abstraction of a H radical from thiophenol afford the product 279.
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. 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.