

[A0047]

Intramolecular Cycloaddition of Imines of Cysteine Derivatives

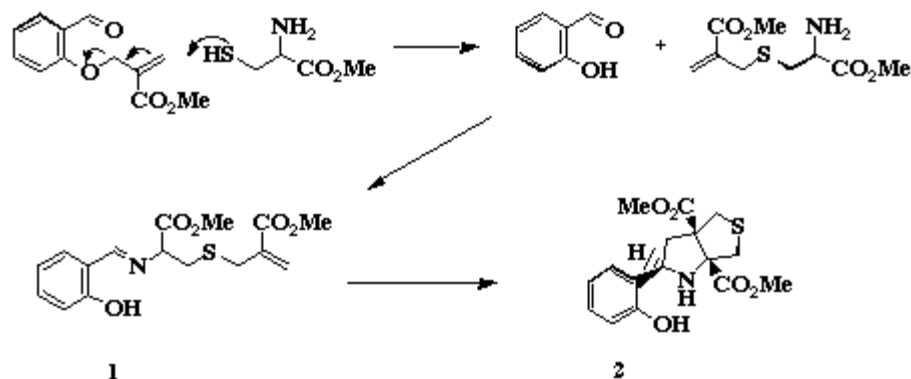
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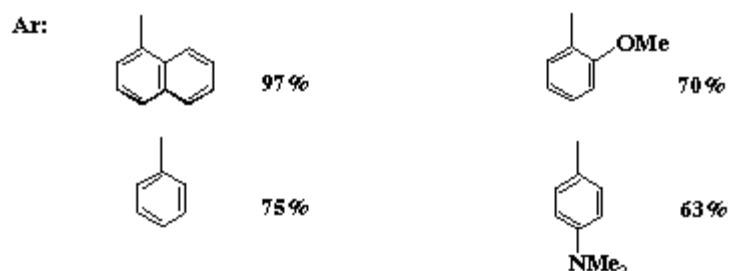
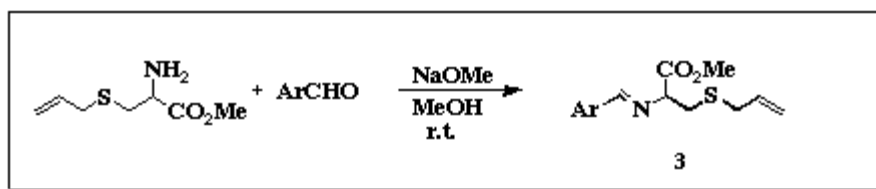
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Introduction

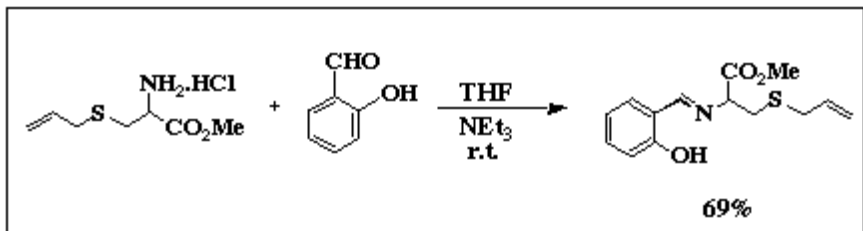
The intramolecular 1,3-dipolar cycloaddition is an important method for the construction of ring fused heterocycles. The prototropic generation of azomethine ylides from imines of α -amino acids esters is an example of this type of process. [1] We have previously reported the synthesis of tetrahydro-1*H*-thieno[3,4-*b*]pyrrole **2** through an intramolecular 1,3-dipolar cycloaddition of the azomethine ylide which was generated from the Schiff base **1** by proton transfer. [2] The structure of compound **2** was established by X-ray crystallography. Grigg and colleagues have also reported two examples of intramolecular dipolar cycloaddition of azomethine ylides derived from Schiff bases of *S*-allylcysteine methyl ester.¹ We decided to further study this cycloaddition reaction in order to extend it as a methodology of synthesis of thieno[3,4-*b*]pyrrole derivatives.



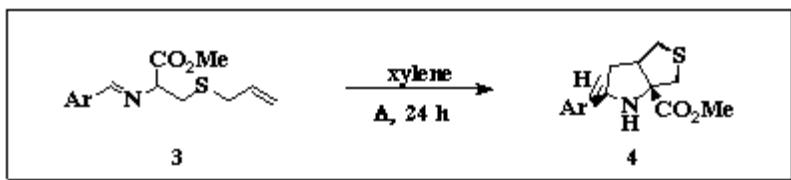
S-Allyl cysteine methyl ester was converted into the corresponding imines in good yield by condensing with a range of aromatic aldehydes in a solution of NaOMe/MeOH at room temperature.



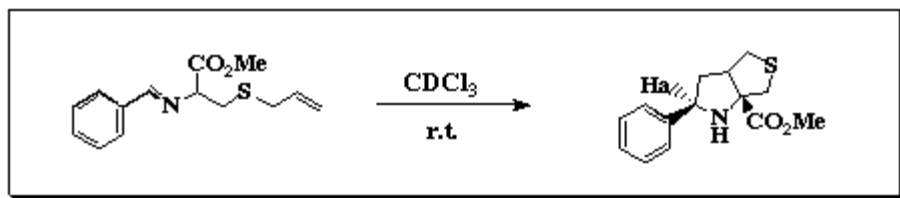
The reaction conditions described above are not suitable for the condensation of salicylaldehyde with S-allylcysteine methyl ester and a complex mixture was obtained. Instead condensation was carried out in THF in the presence of NEt₃ leading to the corresponding imine in good yield.



Each of the imines was dissolved in xylene and the solution was heated under reflux over 24 hours allowing the generation of the azomethine ylides which led to the formation of the corresponding cycloadducts through an intramolecular 1,3-dipolar cycloaddition.

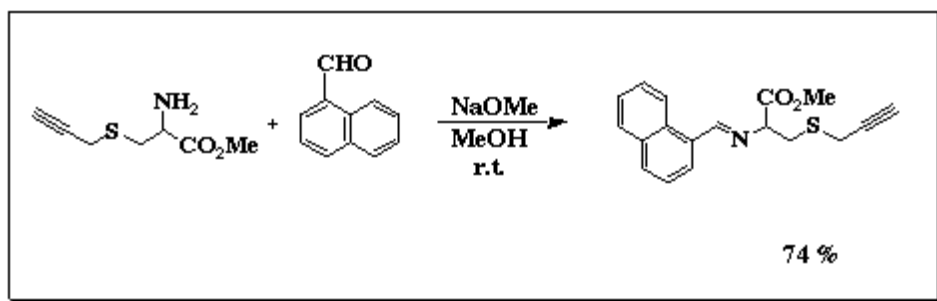


The intramolecular cycloaddition of imine **3** (Ar = Ph) at room temperature was also investigated. A solution of **3** in CDCl₃ was left at room temperature and the reaction followed by ¹H NMR. The yield of the formation of adduct **4** (Ar = Ph) was only estimated from the integration of the triplet assigned to proton Ha (d = 4.53 ppm) vs the singlet of the iminic proton of **3**: after 25 days the adduct was formed in 18% yield, after 76 days in 58% yield and after 130 days in 82% yield. This shows that the intramolecular 1,3-dipolar cycloaddition has a very slow kinetics at room temperature.



	Yield
25 days	18 %
76 days	76 %
130 days	82 %

Attempting to extend these intramolecular cycloaddition reactions *S*-propargylcysteine methyl ester was prepared and condensed with 1-naphthaldehyde giving the imine in good yield.



Heating under reflux a solution of *N*-naphthylidene-*S*-propargylcysteine methyl ester in xylene over 24 hours no reaction occurs and only the imine is recovered. However, when the same imine was dissolved in toluene and heated in the presence of AgOAc and DBU we obtained evidence of formation of a cycloadduct.

Conclusion

Azomethine ylides were generated from Schiff bases of *S*-allylcysteine methyl ester and its intramolecular 1,3-dipolar cycloaddition was performed. A range of thieno[3,4-*b*]pyrrole derivatives was obtained in good yield.

Preliminary studies with *S*-propargylcysteine methyl ester indicates the possibility of extending this type of cycloaddition to different internal dipolarophiles.

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References

- [1] a. R. Grigg, *Chem. Soc. Rev.*, **1987**, 16, 89-121. b. R. Grigg; P. Armstrong, *Tetrahedron*, **1989**, 45, 7581-7585.
- [2] James V. Barkley, Thomas L. Gilchrist; António M. d'A. Rocha Gonsalves; Teresa M. V. D. Pinho e Melo, *Tetrahedron*, **1995**, 51, 13455-134.60.

Comments

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