[a031]

DIMERIC ANHYDRO BASES FROM BENZOTHIAZOLE DERIVATIVES

José Cabrera, Mateo Alajarín, Aurelia Pastor

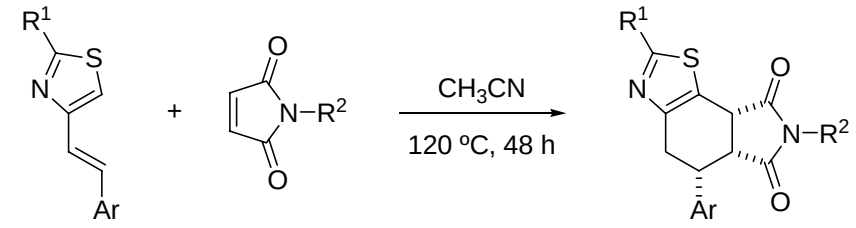
Departamento de Química Orgánica, Facultad de Química
Universidad de Murcia, Campus de Espinardo
E-30.100 Murcia, Spain

Abstract

In order to develop a novel strategy for the synthesis of aminothiol derivatives, the cycloadducts obtained from the reaction of 4-alkenylthiazoles with *N*-substituted maleimides and similar products where the central ring is totally oxidized, were used as starting materials in the sequence *N*-methylation, reduction and hydrolytic cleavage of the thiazole ring. However, instead of the expected aminothiol derivative, a dimeric anhydro base was isolated in the last step. The mechanism implies the formation of a thiazolium cation which evolves to the dimeric anhydro base under the basic conditions.

Introduction

4-Alkenylthiazoles behave as dienes in Diels-Alder reactions by means of the endocyclic C=C bond and the exocyclic double bond [1]. 4-Alkenylthiazoles **1** react towards maleimides to form adducts **2** in excelent yields (Scheme 1, Table 1). The formation of **2** may be explained considering a [4+2] cycloaddition in the first step followed by 1,3-migration of a hydrogen atom. The last process is favored by the rearomatization of the thiazole ring.



1 **2**

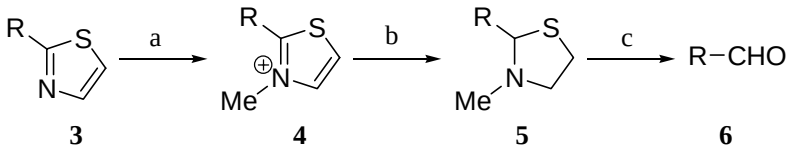
Ar = *p*-ClC$_6$H$_4$

Scheme 1

Table 1			
R^1	R^2	Product	2 (%)
Ph	Ph	**a**	95
Me	Ph	**b**	91
Me	Et	**c**	88

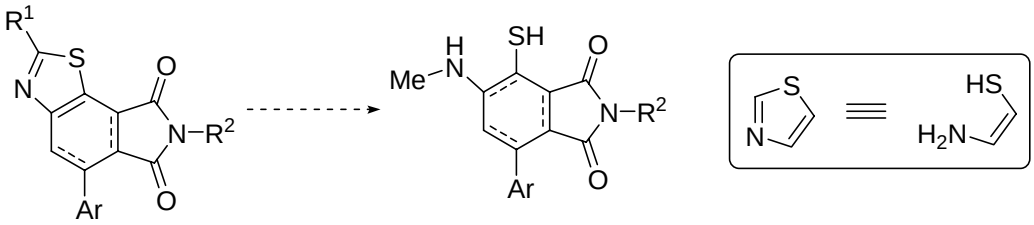
Objectives

The thiazole ring has been used succesfully as a carbonyl equivalent [2]. This transformation may be achieved by a sequence of three reactions: a, *N*-methylation of the thiazole ring; b, exhaustive reduction of the *N*-methylthiazolium salt **4** to the thiazolidine **5**; and c, hydrolysis of **5** to the corresponding aldehyde (Scheme 2).



Scheme 2

We planned to use this strategy to achieve the hydrolytic cleavage of the thiazole ring in cycloadducts **2** and similar products where the central ring is totally oxidized (Scheme 3). In this sequence the thiazole ring may be considered as a 1,2-aminothiol synthon.

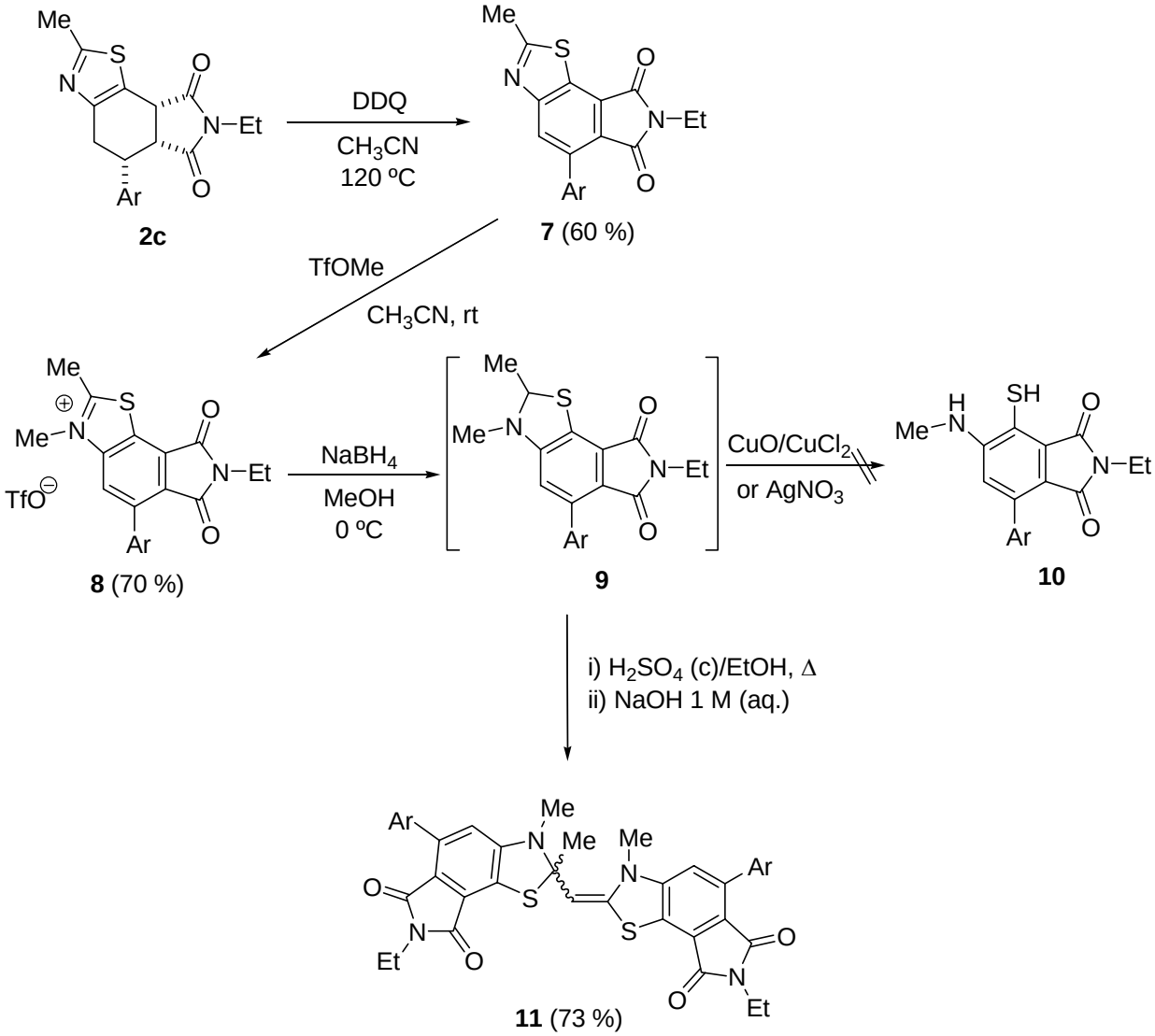


Scheme 3

Results and discussion

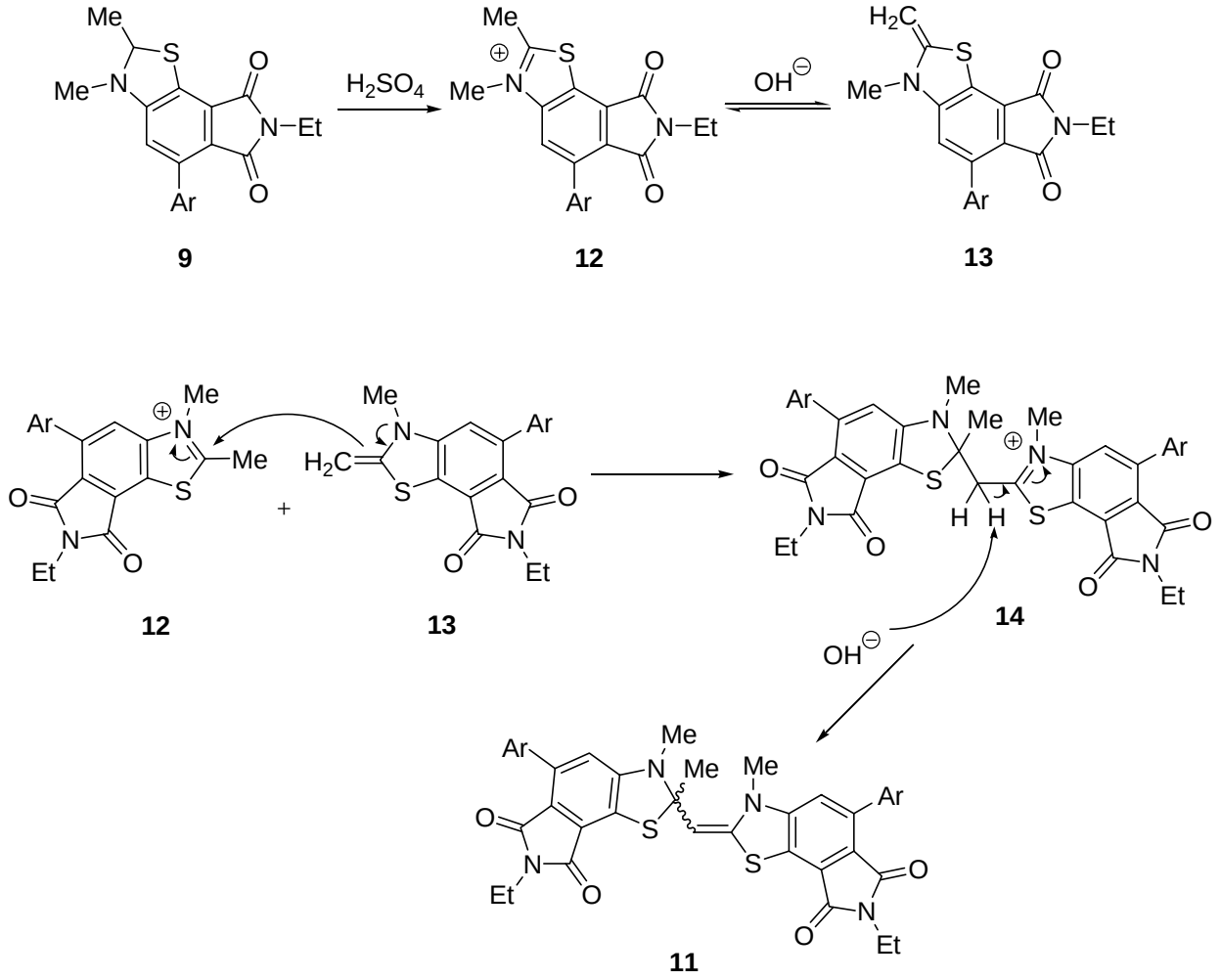
Following a similar route to that shown in Scheme 2, the cycloadduct **2c** was allowed to react with methyl triflate (not shown) but the reduction of the corresponding *N*-methylated derivative with $NaBH_4$, and further hydrolysis with $AgNO_3$ or $CuCl_2$-CuO did not afford the expected aminothiol. By contrary, the results showed that the thiazolidine intermediate was very unstable and easily oxidizable. Thus, the sequence shown in Scheme 2 was accomplished by using the oxidized cycloadducts as starting materials.

First, the cycloadduct **2c** was oxidized with DDQ in acetonitrile at 120 ºC in a sealed tube giving **7** in 60 % yield (Scheme 4). The *N*-methylation of the benzothiazole derivative **7** with methyl triflate in acetonitrile led to the salt **8** in 70 % yield. The reduction of **8** with $NaBH_4$ afforded the *N*-methylthiazoline derivative **9** which was reacted in situ with $CuCl_2$-CuO [3] or alternatively with $AgNO_3$ [4]. Unfortunately, compound **9** was recovered under both reaction conditions. Unexpectedly, when we carried out an hydrolysis attempt in the presence of concentrated sulfuric acid, the dimeric product **11** was obtained.



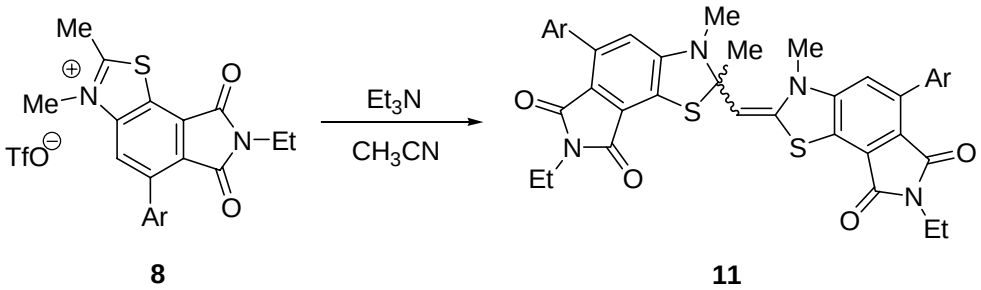
Scheme 4

This result is not unprecedented. It has been reported that 2-methylbenzothiazolium salts form dimers of analogous structures when they are submitted to basic conditions [5]. The mechanism is well established in the literature. Thus, the formation of the dimer **11** may be explained by the sequence of events depicted in Scheme 5. First, the intermediate **9** would be oxidized under the acidic reaction conditions to give the thiazolium cation **12**. Under basic conditions the cation **12** would be in equilibriun with its anhydro base **13**. The anydro base **13** would react as a nucleophile with a second molecule of the thiazolium cation **12** to give the product **14** which would be deprotonated by a hydroxide anion affording the dimeric anhydro base **11**.



Scheme 5

The involvement of the thiazolium derivative **12** as intermediate is supported by the fact that the reaction of the triflate **8** with triethylamine gave immediately the dimer **11** (Scheme 6).



Scheme 6

Conclusions

☑ The essayed reaction conditions for the methylation-reduction-hydrolysis sequence are not convenient for accomplishing the thiazole ring cleavage in the adducts **2c** and **7**. Other alternatives are currently under investigation.

☑ The benzothiazolium salt **8** affords the dimer **11** under basic conditions by the mechanism detailed above.

References

[1] Communication to ECSOC-8.

[2] a) E. J. Corey, D. L. Boger, *Tetrahedron Lett.* **1978**, 5. b) E. J. Corey, D. L. Boger, *Tetrahedron Lett.* **1978**, 13. c) A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, *Angew. Chem. Int. Ed. Engl.* **1986**, *25,* 835. d) A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, P. Pedrini, *J. Org. Chem.* **1989**, 54*,* 693.

[3] A. Dondoni, A. Marra, D. Perrone, *J. Org. Chem.* **1993**, 5*8*, 275.

[4] A. Dondoni, A. Marra, *Tetrahedron Lett.* **2003**, *44*, 13.

[5] a) G. H. Alt, *J. Org. Chem.* **1967**, *33*, 2858. b) J. K. Elwood, *J. Org. Chem.* **1973**, *38*, 2425.

Acknowledgements

This work was supported by MEC-FEDER (Project CTQ2005-02323/BQU) and the Fundación Séneca-CARM (Project 00458/PI/04). J. C. and A. P. thank to the *Ministerio de Educación y Ciencia* of Spain for a fellowship and for a *Ramón y Cajal* contract, respectively.