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[A018]

A CHEMODIVERGENT ISSUE IN THE REACTIONS OF 4-ALKENYLTHIAZOLES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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Introduction

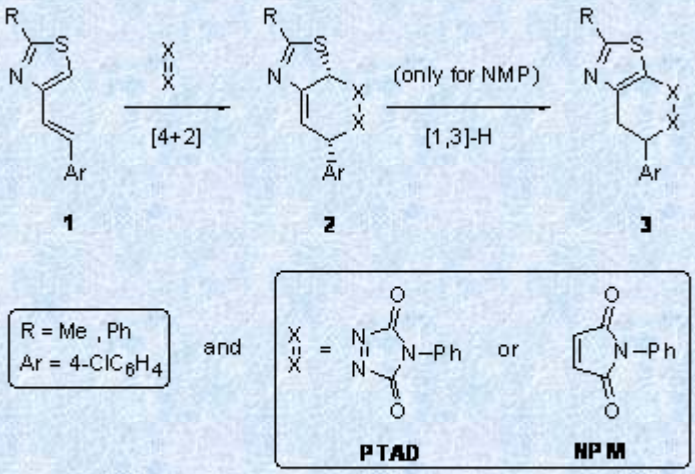
4-Alkenylthiazoles may participate as dienes in Diels-Alder reactions by means of the endocyclic C=C bond and that placed at the side chain (Figure 1).

1

Figure 1

In our hands the reaction of **1** with PTAD led to the corresponding [4+2] adducts **2** in quantitative yields (Scheme 1). [1] [2] When the thiazoles **1** were allowed to react with NPM, only the tetrahydrobenzothiazoles **3** were isolated. The formation of **3** may be explained considering a [4+2] cycloaddition in the first step followed by 1,3-migration of a hydrogen atom. The last

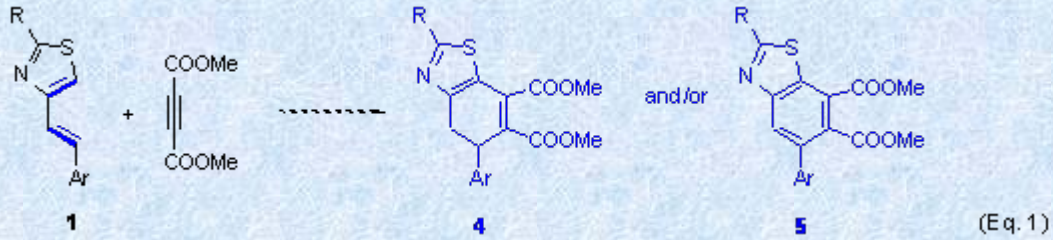
process is favored by the rearomatization of the thiazole ring.



Scheme 1

Objectives

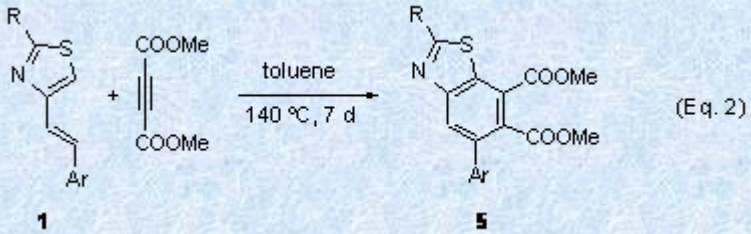
To expand the scope of this new reaction we planned to investigate the reaction of 4-alkenylthiazoles **1** with dimethyl acetylenedicarboxylate (DMAD). Following an analogous mechanism to the other dienophiles tested (PTAD and NPM), DMAD may react with **1** to give the corresponding dihydrobenzothiazoles **4** or the benzothiazoles **5** if spontaneous dehydrogenation under the reaction conditions would take place (Eq. 1).



(Eq. 1)

Results and discussion

The 2-phenyl and 2-methyl-4-alkenylthiazoles **1** were allowed to react with DMAD in toluene at 140 ºC in a sealed tube for 7 days. Under these reaction conditions the benzothiazoles **5** were isolated in moderate yields (Eq. 2 and table 1). Shorter times of reaction or lower temperatures led to low conversions.

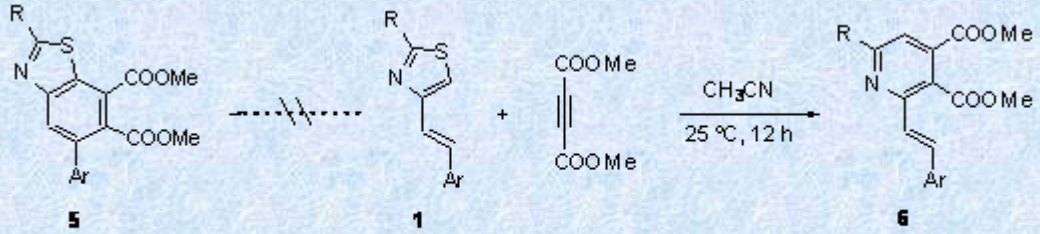


(Eq. 2)

Table 1

R	Ar	5 (%)
Ph	4-MeC$_6$H$_4$	65
Me	4-ClC$_6$H$_4$	25

However, when the 2-amino substituted thiazoles **1** were allowed to react with DMAD the isolated products were not the expected benzothiazoles **5** but the tetrasubstituted pyridines **6**, which were obtained in moderate yields (Scheme 2 and table 2).[3] Notably, the 2-aminothiazoles were much more reactive compared to the 2-methyl and 2-phenyl derivatives (Eq. 2). Thus, for the 2-amino substituted thiazoles lower temperatures (25 ºC versus 140 ºC) and shorter reaction times (12 h versus 7 days) were required.

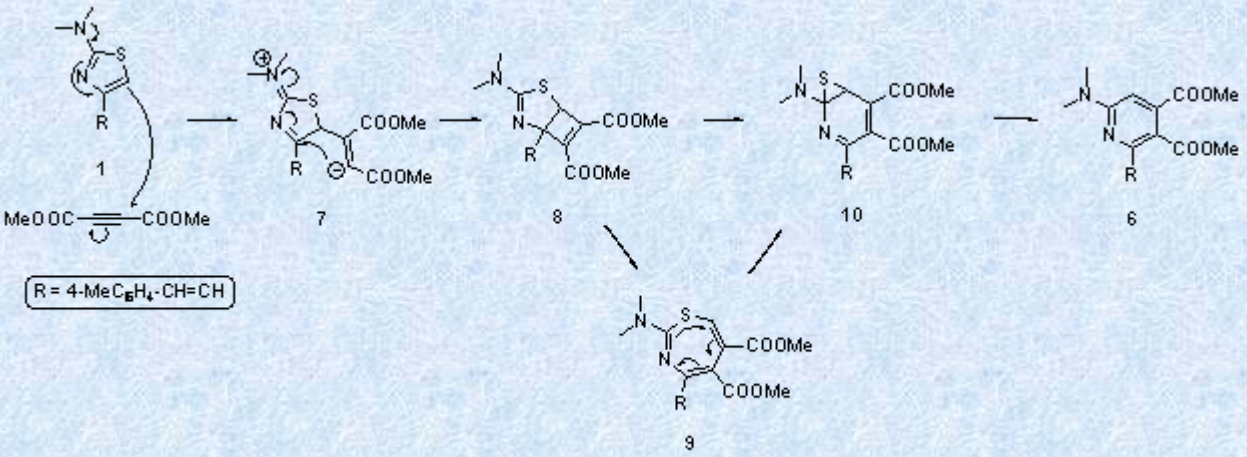


Scheme 2

Table 2

R	Ar	6 (%)
NHPh	4-MeC_6H_4	36
NMe_2	4-MeC_6H_4	70

The formation of the tetrasubstituted pyridines **6** may be explained by the mechanism depicted in Scheme 3. The 5 position at the thiazole ring is activated by the presence of the amino group. In these terms, the nucleophilic attack of the thiazole derivative at the 5 position to the DMAD would give the intermediate **7**. The zwitterionic species **7** would evolve by a ring closure to give the bicycle **8**. The opening of the cyclobutene ring in **8,** either directly or through the formation of the 1,3-thiazepine **9**, would lead to the intermediate **10**. Finally, the pyridine **6** would be formed from **10** by sulfur extrusion.



Scheme 3

Conclusions

☑ The reactions of 2-methyl and 2-phenyl-4-alkenylthiazoles **1** with DMAD lead to the benzothiazoles **5** in moderate yields through a [4+2] cycloaddition followed by dehydrogenation.

☑ The reactions of 2-amino-4-alkenylthiazoles **1** and DMAD give under softer conditions the tetrasubstituted pyridines **6**. The formation of **6** may be rationalized in terms of an stepwise mechanism starting from the nucleophilic attack of the thiazole ring through its 5 position to the acetylenic carbon atom of the DMAD.

☑ Notably, the nature of the substituent at 2-position of the thiazole ring modulates the reactivity towards DMAD leading to alternative products.

References

[1] Communication to “2nd Mediterranean Meeting on Organic Chemistry”, Almería (Spain), 2004.

[2] Communication to ECSOC-8.

[3] Compounds **6** have been fully characterized by their spectroscopic data.

Acknowledgements

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