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Tetrahedron 62 (2006) 6398–6404
Tetrahedron

Access to substituted thiapyrrolizidinones and fused pyridones using the domino *N*-acyliminium-thionium equilibrium/1,3-dipolar cycloaddition/desulfurization cyclization cascade

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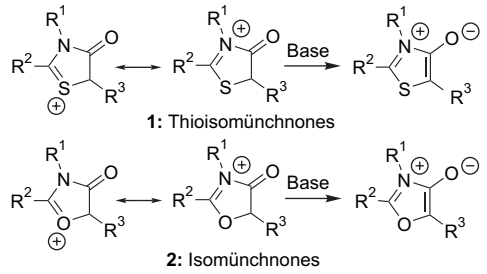
Received 10 March 2006; revised 5 April 2006; accepted 6 April 2006
Available online 6 May 2006

Abstract—Substituted thiapyrrolizidinones and fused pyridones, and quinolizinones were reported efficaciously from suitable thioamides in yields ranging from 30% to 65%. The reaction proceeded in a one-pot procedure as cascade process by the intramolecular 1,3-dipolar cycloaddition of thioisomünchnones followed by desulfurization of the adducts. During these investigations, the mechanistic aspects of the process were also discussed.

1. Introduction

Thioisomünchnones conventionally named 1,3-thiazolium-4-olates (**1**) and belonging to a five-membered mesoionic systems are receiving less attention compared to their oxygen homologues as isomünchnones (1,3-oxazolium-4-olates (**2**)), (Scheme 1).[1] Since the pioneering work by Potts and co-workers given on their syntheses and reactivity,[2] it has been demonstrated now that these species constitute powerful intermediates in the synthesis of complex nitrogen-containing heterocycles.[3] In particular, they offer rapid access to different heterocyclic compounds containing a pyridone nucleus useful in natural products syntheses[4] as well as β-lactams, polyhydrothiophenes in chiral form or not, thiiranes, thiophenes, etc.[4,5]



Scheme 1. Mesoionic five-membered heterocyclic mesomeric betaines.

These mesoionic ring systems, which are easily prepared by the reaction of *N*-monosubstituted thioamides with α-haloacyl halides in the presence of 2 equiv of triethylamine are stabilized by the conjugation effect as shown in Scheme 1 (thionium ion ↔ *N*-acylimiunim cation ↔ mesoionic specie). In addition, some extra stabilization could arise from the conjugation with an exocyclic electron rich aromatic or heteroaromatic system when R^2 is an aryl or heteroaryl group. As a consequence, these mesomeric betaines exhibit an interesting synthetic potential, which could be attributed in addition to (a) the interesting physical properties they possess,[6] and importantly (b) the propensity of its thio-carbonyl ylide dipole to undergo 1,3-dipolar cycloaddition with a range of double and triple-bond dipolarophiles.

Due to the high number of natural and unnatural biological active molecules containing the thiapyrrolizinone[7] and quinolizinone[8] subunits, the use of that approach is still of continuous interest in organic synthetic chemistry. Among the most known naturally occurring alkaloids, oxogambirtannine (**3**)[9] and sempervilam (**4**)[10] belonging to the yohimboid alkaloids, constitute one of the major subgroups of the indole class. If these structures have not yet shown any biological properties, mitragynaline (**5a**, R=OMe) as an indole alkaloid,[11] was isolated from the Malaysian *Mitragyna speciosa korth* plant. This is used in the Malay Peninsula as a stimulant like coca or as substitute from opium.[12] Moreover other tricyclic benzo- and thieno[*a*]quinazolines developed by investigators at Hoffman La-Roche, Ltd have been shown to be excellent alternatives to molecules with benzodiazepines scaffolds for the treatment of anxiety and sleep disorders.[13]

Keywords: Thioisomünchnone; 1,3-Dipolar cycloaddition; Thioamide; Heterocycle; Domino process; Lawesson's; Thionation; One-pot procedure.
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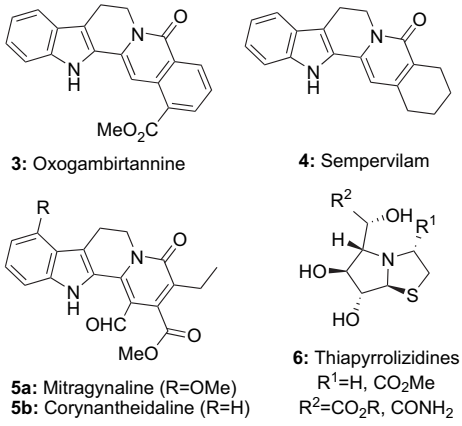
0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.04.032

On the other hand, pyrrolo[2,1-*b*]thiazoles are rare scaffolds since only few reports are done in the literature. In this sense, whatever, two related structures were reported by the Padwa group using that strategy[4,14] while others described some thia-analogues of the glycosidase inhibitors polyhydroxylated pyrrolizidinones (**6**, R^1=H and CO_2Me; R^2=CO_2R and $CONH_2$).[15,16] The strategy used in these cases was based on the cyclodehydration of thiazolidines bearing an hydroxymethyl branched group[15] and an unexpected ring contraction of 7,5-fused bicyclic thiazolidine-lactams,[16] respectively.

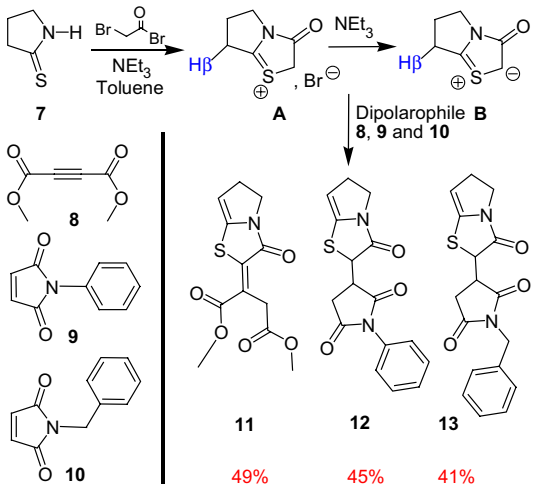
2. Results and discussion

As part of a long-term project dealing with our search for a simple synthetic route to heterocyclic homologues of the above structures (Scheme 2), which could be applicable to the synthesis of different condensed five and six-membered azacycles, we explore in this paper the intramolecular 1,3-dipolar cycloaddition of new thioisomünchnones with systematically three different dipolarophiles. This process proceeds in a one-pot procedure and result in the formation of new substituted 1,3-thiazolidinones and fused pyridones, heterocyclic scaffolds with promising biological activity.



Scheme 2. Representative structures containing thiapyrrolizinone and quinolizinone subunits.

Because of the use of thioisomünchnone of type **B** as a dipole, in cycloaddition reactions remains unreported, we first investigated the behavior of this thioisomünchnone, derived from pyrrolidine-2-thione (**7**), in the intramolecular 1,3-dipolar cycloaddition conditions as shown in Scheme 3. For this purpose, the requisite pyrrolidine-2-thione (**7**) was obtained in one step in quantitative yield by thionation of pyrrolidine-2-one with 1 equiv of Lawesson's reagent in dry toluene at reflux for 3 h[17] and the dipolarophile chosen as the reaction partner for optimizing conditions was the methyl acetylenedicarboxylate (**8**). So, after intensive screening of reaction conditions,[18] the use of 1.1 equiv of 2-bromoacetyl bromide, 2.0 equiv of dry triethylamine as a base, 1.5 equiv of suitable dipolarophile, and anhydrous toluene as solvent was found to be the most effective combination for obtaining representative results. Under these conditions, pyrrolidine-2-thione (**7**) with 2-bromoacetyl bromide and triethylamine led to thionium salt **A** then mesoionic five-membered **B**, which after reaction with dipolarophile **9**, led to the structure containing thiapyrrolizin-one ring **11** in 49% yield (Scheme 3).



Scheme 3. Scheme leading to new structures containing thiapyrrolizinone nucleus as **11**, **12**, and **13** from betaine **B**.

Having the best conditions in hand, we examined next the reaction of the same substrate as above with 2-bromoacetyl bromide and other dipolarophiles in the presence of triethylamine (Scheme 3). In this context, the commercially available *N*-phenylmaleimide (**10**) and *N*-benzylmaleimide (**11**) were found to be employable efficaciously without the change of the course of the cascade process as well as the reaction yields. Indeed, the reaction products, identified as thiapyrrolizinones **12** and **13**, were isolated in 45% and 41% yields, respectively, comparables to that obtained for the thiapyrrolizinone derivative **11**.

As shown in Scheme 4, the suggested reaction mechanism illustrates three pathways that appear possible. Initially formed thionium cation **A**, in equilibrium with corresponding *N*-acyliminium one **C**, would lead with triethylamine to either the thiapyrrolizinone **14** or the carbanion **G** via mesoionic five-membered heterocyclic mesomeric betaines **B** and **D**, in equilibrium. No traces of product **14** were found in the reaction mixture examined by TLC before addition of a second equivalent of triethylamine, a dipolarophile as well as at the end of the reaction process before any purification. Also, no trace of pyridone component **15** as well as corresponding thia-bridged products **F**, which would be formed by the intramolecular 1,3-dipolar cycloaddition of 3-thiazolium-4-olate salt (**B** or **D**, see Scheme 4), was observed. Therefore, these thioisomünchnones species afforded the thiapyrrolizinones **11**, **12**, and **13** upon abstraction of the hydrogen atom at β-position of nitrogen and/or sulfur atom(s) in the intermediate (**A**↔**C**) or (**B**↔**D**) followed in an ultimate stage by addition of a dipolarophile and protonation of the resulting carbanion. Interestingly, the process seems to be general and the key step seems to be the hydrogen abstraction.

The ^{1}H NMR spectra of thiapyrrolizinones **11**, **12**, and **13** are characterized by having the olefinic proton of the dihydropyrrole nucleus in the aromatic region (from δ=6.98 up to 7.35 ppm). This was coupled with methylene protons at β-position of the dihydropyrrole ring and in the case of