Tetrahedron 67 (2011) 9541–9554

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

endo-Mode cyclizations of vinylogous *N*-acyliminium ions as a route to the synthesis of condensed thiazolidines

Milovan Stojanović [a,b], Rade Marković [a,c], Erich Kleinpeter [b], Marija Baranac-Stojanović [a,b,c,*]

[a] *Center for Chemistry ICTM, P.O. Box 473, 11000 Belgrade, Serbia*
[b] *Chemisches Institut der Universität Potsdam, Karl-Liebknecht Str. 24-25, D-14476 Potsdam (Golm), Germany*
[c] *Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 158, 11000 Belgrade, Serbia*

ARTICLE INFO

Article history:
Received 12 July 2011
Received in revised form 14 September 2011
Accepted 3 October 2011
Available online 10 October 2011

Keywords:
Vinylogous *N*-acyliminium ion
endo-Mode cyclization
Condensed thiazolidines
Quantum chemical calculations

ABSTRACT

endo-Mode cyclizations of vinylogous *N*-acyliminium ions incorporating heteroatom-based nucleophiles have been examined as a route to the synthesis of condensed thiazolidines. The scope of these reactions and stereochemical outcome are discussed and explained using quantum chemical calculations.

1. Introduction

Iminium ions have proven to be valuable intermediates in organic synthesis for the formation of carbon–carbon and carbon–heteroatom bonds. Indeed, the well-known Mannich reaction[1] and its intramolecular variant—the Pictet–Spengler reaction,[2] used for a long time as α-aminoalkylation reactions, are based on the reactive iminium species. Iminium ion cyclizations have been widely exploited as a powerful method for the construction of a huge variety of heterocyclic systems.[3] Diverse nucleophiles, such as π-nucleophiles (aromatic rings, carbon–carbon double, and triple bonds), σ-nucleophiles and heteroatom-based nucleophiles, have been used to react with various acyclic and cyclic iminium ions in both *exo*- and *endo*-mode cyclizations (Fig. 1). Heterocycles produced via the addition of heteroatoms as nucleophiles onto the iminium ions not only are well-known and important compounds, particularly in the field of medicinal chemistry, but also represent stable potential iminium ions equivalents due to reversibility of the addition process. Despite the fact that, according to Baldwin's rules,[4] 5-*endo*-*trig* cyclizations are classified as 'unfavoured' for the first-row elements,[4b] they can occur with iminium ions as reactive species.[3a–c,h,j,5]

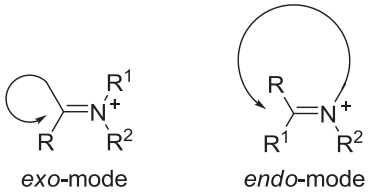


Fig. 1. *exo*- and *endo*-Mode cyclizations.

Suitable structural variations in the iminium ion precursor, like introduction of a second heteroatom, enlarges the scope of the iminium ion methodology. For example, cyclizations involving thiazolidine-based iminium ions can result in the formation of a variety of derivatives of interesting pharmacological structure.[6] In addition, further desulfurization of thiazolidine-containing polycycles is a valuable method for synthesis of various ring structures, some of which are not easily accessible by other routes.[6c,7]

The iminium ions can be divided into two main categories: *N*-alkyl-[3a] (R^3, R^4=alkyl, aryl, Fig. 2) and *N*-acyliminium ions[3b,c] (R^3=alkyl, aryl, R^4=COR, CO_2R, SO_2R, Fig. 2). Introduction of an electron-withdrawing group on nitrogen leads to more electrophilic iminium carbon, which makes *N*-acyliminium ions much more reactive as electrophiles than simple *N*-alkyliminium ions. A subtype of *N*-acyliminium ions with carbon–carbon double bond conjugating an acyl group to nitrogen is referred to as *vinylogous N-acyliminium ions* (Fig. 3). Literature covering this type of iminium

* Corresponding author. Tel.: +381 11 3336740; fax: +381 11 2636061; e-mail address: mbaranac@chem.bg.ac.rs (M. Baranac-Stojanović).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.10.011

ions is rather scarce, with just a few reports published thus far. It has been shown that they can react with added nucleophiles,[8] or initiate ring-closing reaction with π-nucleophile, such as an olefin[9] or aromatic ring.[10]

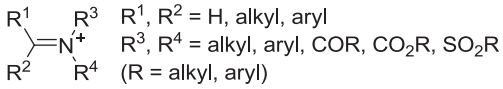


Fig. 2. *N*-Alkyl and *N*-acyliminium ions.

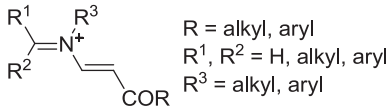
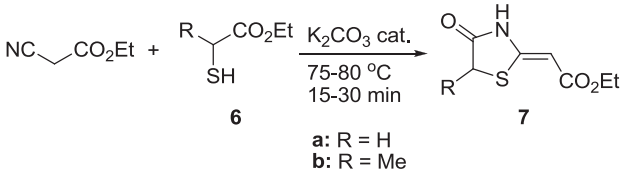


Fig. 3. Vinylogous *N*-acyliminium ions.

In the course of our studies on the reactivity of 2-alkylidene-4-oxothiazolidines we have observed that vinylogous *N*-acyliminium ion **3** derived from compound **1** can undergo cyclization reaction in a 5-*exo* mode giving rise to bicyclic product **5**, albeit in low yield (Scheme 1).[11] The iminium ion **3** is formed from the hydroxy derivative **2**, produced by the regioselective reduction of one carbonyl of the vinylogous imide function. The resistance of another carbonyl to reduction is considered to reside in its deactivation due to the push–pull effect of the carbon–carbon double bond.[12] Now, the iminium function enhances the electrophilicity of the ester group in **3** allowing its reduction to **4**, even at rt.[13] Subsequent 5-*exo*-*trig* cyclization affords the *cis*-fused tetrahydrofurothiazolidine **5**. This finding prompted us to further explore the ability of these new vinylogous *N*-acyliminium ions to participate in cyclization reactions with suitably positioned nucleophiles. We examined reactions with a range of heteroatom-based nucleophiles in both *endo*- and *exo*-mode. Herein, we present the results of *endo*-mode reactions together with quantum chemical calculations used to rationalize the experimental observations.

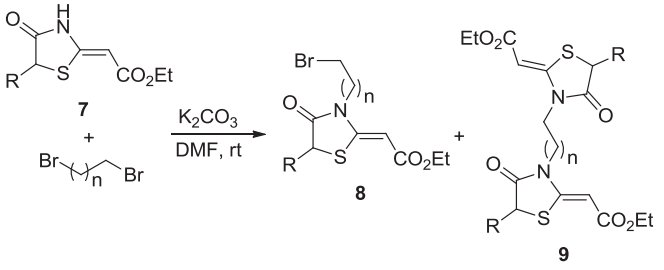
Table 1
Comparison of synthesis of 4-oxothiazolidines **7** with and without solvent



Product	Reaction conditions and yield[a] (%)	
7a-*Z* (R=H)	EtOH, reflux, 5 h (67)	No solvent, 75–80 °C, 30 min (87)
7b-*Z* (R=Me)	EtOH, reflux, 6 h (42)	No solvent, 75–80 °C, 15 min (76)

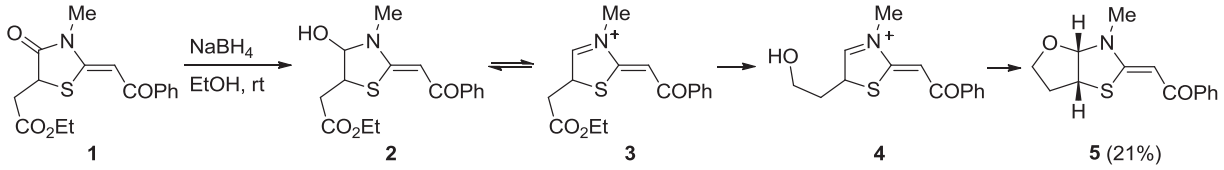
[a] Yield of isolated products.

Table 2
N-Alkylation of 4-oxothiazolidines **7** with α,ω-dibromides



R	*n*	Time (h)	Product **8**[a] (%)	Dimer **9**[a] (%)
H	1	5	**8a** (72)	/
Me	1	5	**8b** (82)	**9a** (6)
H	2	2	**8c** (70)	**9b**(18)
Me	2	2.5	**8d** (70)	**9c** (21)
H	3	4	**8e** (83)	**9d** (4)
Me	3	1.5	**8f** (80)	**9e** (7)

[a] Yield of isolated products.



Scheme 1.

2. Results and discussion

2.1. Synthesis of 4-oxothiazolidines

Starting 4-oxothiazolidines **7** were prepared by the base-catalyzed reaction of ethyl cyanoacetate and α-mercapto esters **6**, with a slight modification of our published procedure for the synthesis of 4-oxothiazolidine compounds.[14] In contrast to the published procedure, these syntheses were run without solvent, which resulted in significant shortening of the reaction time and increase in the yields of the products (Table 1). The products were obtained exclusively as *Z* isomers.[15]

2.2. Cyclization reactions

Preparation of precursors for the *endo*-mode cyclizations began with the N-alkylation of 4-oxothiazolidines **7** with α,ω-dibromides[16] (Table 2). *N*-Bromoalkyl derivatives **8** were obtained along with the dimeric products **9**. Thus, it was necessary to employ 4–5.4 molar excess of the alkylating agent to suppress the dialkylating process and effect the best yields of **8**.

The obtained alkyl bromides **8** were then converted into precursors possessing O, S, or N as a nucleophilic atom (Scheme 2 and Table 3). Hydrolysis using 0.75 M DMF/H_2O solution of HCl, based on the method of Geluk and Schlatmann,[17] afforded alcohols **11a–e** in moderate to high yields (51–92%). The observed experimental rates of hydrolysis (Scheme 2), which decrease in the order (n=1)>(n=2)>(n=3), points to the neighboring-group participation of carbonyl oxygen of the lactam group. When n=1, formation of a favorable five-membered cyclic intermediate **10** can facilitate the hydrolytic reaction. When n=2 and 3, the participation of carbonyl oxygen is diminished due to the greater loss of entropy accompanying the formation of six- and seven-membered rings, resulting in much longer reaction times (n=1 (3 h); n=2 (19–21 h); n=3 (24 h)). Substrates **12a–f** containing sulfur as a nucleophile were prepared in high yields (93–100%) by the reaction of bromides **8** with KSAc in acetone, at rt.[18] They were deprotected with NaOEt/EtOH[19] prior to the formation of iminium ions (see Experimental section). Two type of precursors with nitrogen-based