Tetrahedron Letters 50 (2009) 178–181

Contents lists available at ScienceDirect

Tetrahedron Letters

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

An easy approach to α,β-unsaturated δ-thiolactams via a RCM and thionation one-pot procedure

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ARTICLE INFO

Article history:
Received 17 September 2008
Revised 21 October 2008
Accepted 22 October 2008
Available online 25 October 2008

Keywords:
Dialkenoic amides
RCM
Lawesson's reagent
Isomerization
3,6-Dihydro-1*H*-pyridine-2-thione
5,6-Dihydro-1*H*-pyridine-2-thione
Quinolizidine-4-thione

ABSTRACT

An easy approach to mono- and bicyclic derivatives of 5,6-dihydro-1*H*-pyridine-2-thione via a one-pot ring closing metathesis (RCM) of dialkenoic amides and thionation using Lawesson's reagent, followed by isomerization of the 3,6-dihydro-isomer (if necessary), is described. The appreciable differences in the reactivity of diallylic amides in RCM reactions are discussed.

α,β-Unsaturated δ-thiolactams have been recognized as good Michael acceptors. They form C–C bonds in reactions with C-nucleophiles: alkyllithium, alkylmagnesium[1,2] lithium enolates[3] and with aliphatic nitro-compounds in the presence of a base as catalyst.[4] In contrast to nonactivated α,β-unsaturated δ-lactams, the analogous thiolactams react easily with N- and S-nucleophiles, affording 4-substituted δ-thiolactams.[5] Due to their good reactivity in 1,4-addition reactions and the acidity of the C-3 protons being higher than those of the analogous lactams, α,β-unsaturated δ-thiolactams can be used to synthesize 4-mono- or 3,4-disubstituted piperidines. Exploring our concept of the functionalization of piperidine rings via α,β-unsaturated δ-thiolactams, we had previously published the stereoselective synthesis of trans-fused bicyclic 2-piperidinone derivatives (octahydro[2]pyridinones)[6] and 4-isothiocyanato-2-piperidinones.[7] Moreover, α,β-unsaturated δ-thiolactams have been found to be valuable substrates in the synthesis of chiral pyrrolidin-2-ylidene carboxylates[4] and could be important pharmaceuticals, since a derivative of 2-piperidinecarboxylic acid was found to have a wide spectrum of antitumor activity.[8]

Although 5,6-dihydro-1*H*-pyridine-2-thiones exhibit better reactivity in 1,4-Michael additions than the corresponding lactams, their C=S group is easily converted into other functionalities,[9] indicating their synthetic potential in piperidine synthesis, α,β-unsaturated δ-thiolactams are still unappreciated as starting materials, perhaps due to their low attainability.

The hitherto proposed methods for the preparation of 3,4-unsubstituted α,β-unsaturated δ-thiolactams include thionation of α,β-unsaturated δ-lactams using Lawesson's reagent[5] or introduction of an α,β-double bond into saturated thiolactams via 3-benzenesulfinyl derivatives[6,10] or additions of organolithium(magnesium) reagents to the corresponding 2-thiopyridones and isomerization of the obtained 3,6-dihydro-1*H*-pyridine-2-thiones to α,β-unsaturated isomers with DBU.[11] Unfortunately, these three important synthetic routes are disadvantages. Thionation of α,β-unsaturated δ-lactams using Lawesson's reagent is possible with N,6-disubstituted 5,6-dihydro-1*H*-pyridin-2-ones, while N-substituted α,β-unsaturated δ-lactams with unsubstituted rings decompose under the same reaction conditions for reasons unknown (Scheme 1, right side and Ref. 5). The second method suffers from the poor accessibility of saturated thiolactams, and the third method is limited to the successful synthesis of 6-alkyl(aryl)-substituted derivatives of NH and 6-allyl-, NR- (Me, Bn, Ph) disubstituted derivatives of α,β-unsaturated δ-thiolactams. The above disadvantages have prompted us to find more efficient methods for the synthesis of 6-unsubstituted/substituted N-substituted 5,6-dihydro-1*H*-pyridine-2-thiones. The result is an easy synthetic approach to mono- and bicyclic derivatives of 5,6-dihydro-1*H*-pyridine-2-thiones in a procedure combining ring closing metathesis (RCM) and thionation using Lawesson's reagent in one-pot, followed by isomerization of the 3,6-dihydro-isomers.

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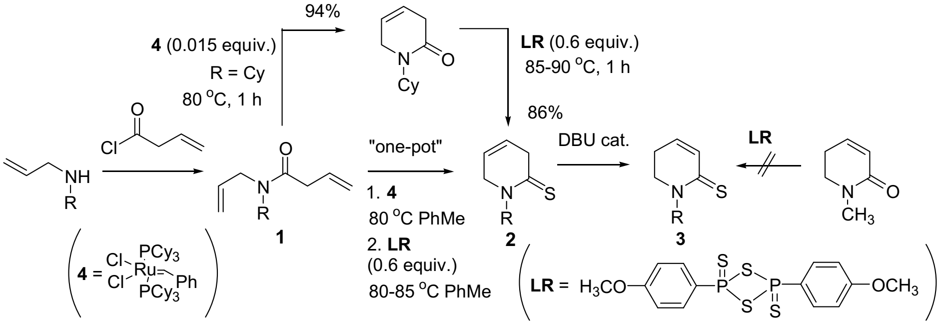
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.113



Scheme 1. Synthesis of NMe, NCy, and NPh-substituted derivatives of 5,6-dihydro-1*H*-pyridine-2-thione by RCM/thionation in one-pot followed by isomerization.

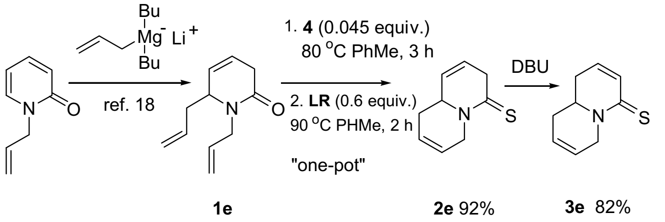
Lawesson's reagent is an effective reagent applied in the conversion of amides into thioamides;[12] however, as mentioned earlier, it cannot be applied for conversion of α,β-unsaturated δ-lactams with unsubstituted rings. Inspired by a recent observation that β,γ-unsaturated δ-thiolactams can be isomerized completely to α,β-unsaturated isomers using DBU,[11] we decided to synthesize α,β-unsaturated δ-thiolactams by treatment of β,γ-unsaturated δ-lactams with Lawesson's reagent followed by isomerization. However, access to the lactam precursor is as an essential point of this strategy. Fortunately, since Grubbs first applied his ruthenium RCM catalyst to the synthesis of unsaturated δ-lactams,[13] a number of publications have appeared describing the synthesis of β,γ-[14] and α,β-[15] unsaturated δ-lactams from open chain precursors or by rearrangement of mixed olefins (domino metathesis).[16] Because the synthesis of β,γ-unsaturated δ-lactams by RCM is well documented, we decided to use this method in our investigation.

Initially, the NH, NMe, NCy, and NPh derivatives of *N*-allyl-3-butenamides were synthesized and submitted to RCM reactions at 80 °C in degassed toluene (Scheme 1, Table 1). For economic reasons, the first generation Grubbs' catalyst (**4**) was applied in RCM and in order to use the minimum amount of catalyst, 0.015 equiv of the catalyst (with respect to **1**) was added to a toluene solution of **1** in order to initiate the reaction, and the same amount of the catalyst was added after each subsequent hour of heating. During the reaction, a stream of argon was slowly bubbled through the solution and the reaction was continued until the substrate was completely consumed (after every half an hour the reaction mixture was analyzed by GC–MS). Surprisingly, different reactivities of the open chain substrates **1**, depending on the NR substituent, were observed in the RCM reactions. The reactions with NMe-(**1b**) and NCy-(**1c**) substituted diallyl amides were fast, and were accompanied by spontaneous evolution of ethylene, leading to complete lactam formation in 30 min after addition of only one portion of the catalyst (0.015 equiv). The NPh derivative required a longer reaction time and a larger quantity of catalyst for complete conversion. Complete conversion of NH diallylic amide **1a** was achieved in 7 h after 0.1 equiv of catalyst had been added; however, no cyclic product was observed by GC–MS analysis (Scheme 1, Table 1). When the RCM reaction was complete, 0.6 equiv of Lawesson's reagent (**LR**) was added, and the reaction mixture was heated at 80–85 °C in the same flask without isolation of the δ-lactams. The resulting mixture was chromatographed twice on silica gel to provide the desired N-substituted β,γ-unsaturated δ-thiolactams **2b–d** in good yields (Table 1). However, in the case of NH amide **1a**, thiolactam formation was not detected.

Obviously, compounds **2b–d** could be prepared by two separate steps as tested with the NCy-substituted derivative, however, the one-pot procedure is much more convenient and effective (Scheme 1).

Finally, the β,γ-unsaturated δ-thiolactams **2b–d** were converted easily to the α,β-unsaturated isomers **3b–d** (Scheme 1, Table 1) using catalytic DBU in acetonitrile.[11,17] The required starting materials **1** were readily obtained from the corresponding allylamines by N-acylation with 3-butenoic acid chloride (Scheme 1).

The same RCM/thionation/isomerization strategy was also applied successfully to *N*,6-diallylic β,γ-unsaturated lactam **1e** providing unsaturated thiolactams **2e** and **3e** possessing bicyclic quinolizidine systems in high yields (Scheme 2). In this case, the *N*,6-diallylic precursor was obtained by addition of lithium allyldibutylmagnesate to *N*-allyl-2-pyridone.[18] Since the thionation of N,6-disubstituted α,β-unsaturated δ-lactams with **LR** is possible[5] and the synthesis of α,β-unsaturated δ-lactams by RCM is also well documented,[15] we decided to test the direct preparation of α,β-unsaturated δ-thiolactams. *N*,6-Diphenyl-5,6-dihydro-1*H*-pyri-



Scheme 2. Synthesis of 1,6,9,9a-tetrahydroquinolizine-4-thione (**3e**) via the one-pot RCM/thionation followed by isomerization.

Table 1
Ratio of rotamers of **1**, reaction conditions and yields of **2** and **3**

Entry	Amide **1** (R)	Ratio of rotamers[a] *trans*-diallyl/*cis*-diallyl	Equiv of **4**	Time for RCM (h)	Temp [°C]/time [h] for thionation	Conv. of **1**[c] [%]	Yield of **2**[d] [%]	Yield of **3**[d] [%]
1	**1a** (H)	1:0	0.105[b]	7	80/1	>99	0	–
2	**1b** (Me)	1:1	0.015	0.5	80/1	>99	80	86
3	**1c** (Cy)	1:0.6	0.015	0.5	85/1	>99	89	88
4	**1d** (Ph)	1:0	0.075[b]	5	80/0.5	>99	71	81

[a] Estimated by ^1H NMR in $CDCl_3$ or toluene-d_8 solution.
[b] 0.015 equiv of **4** was added at the beginning and after every hour of the reaction.
[c] Conversion determined by ^1H NMR spectroscopy.
[d] Isolated yields.