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Tetrahedron Letters 46 (2005) 2045–2048
Tetrahedron Letters

Cyclizations of 2-alkylthiazolines and 2-alkyloxazolines with α,α-disubstituted diacid chlorides or *N*-(chlorocarbonyl) isocyanate

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Received 15 December 2004; revised 26 January 2005; accepted 26 January 2005

Abstract—Two-step cyclizations of 2-alkylthiazolines or 2-alkyloxazolines with α,α-disubstituted diacid chlorides produce excellent yields of 6,6-dialkyl-2,3-dihydrothiazolo[3,2-*a*]pyridine-5,7-diones and 6,6-dialkyl-2,3-dihydrooxazolo[3,2-*a*]pyridine-5,7-diones in refluxing acetonitrile containing Et_3N. Similar cyclizations using *N*-(chlorocarbonyl) isocyanate in place of diacid chlorides produced 2,3-dihydrothiazolo[3,2-*c*]pyrimidine-5,7-diones or 2,3-dihydrooxazolo[3,2-*c*]pyrimidine-5,7-diones, respectively. Each cyclization proceeded through cyclic ketene-N,X-acetal (X = O or S) intermediates.

2-Alkylthiazolines and 2-alkyloxazolines have long been used in organic synthesis,[1–10] but few reports have appeared on their reactions with acid chlorides.[11,12] We recently demonstrated[13] that 2-methylthiazolines **1** react with 2 equiv of acid chloride to form *N*-acyl-β-keto cyclic ketene-N,S-acetals **3** (Scheme 1). The first equivalent of acid chloride reacts with **1** to form the reactive *N*-acyl cyclic ketene-N,S-acetal intermediate **2**. This intermediate is reactive and nucleophilic due to electron donation from both N and S and reacts further with a second equivalent acid chloride to generate *N*-acyl-β-keto cyclic ketene-N,S-acetals **3**.

We postulated that the nucleophilic *exo*-cyclic methylene carbon of **2** could cyclize to form fused ring compounds **13** if diacid chlorides were initially employed (Scheme 2). Seven successful example reactions were then demonstrated (Table 1) using α,α-disubstituted malonyl chlorides. Furthermore, we successfully extended these cyclizations to 2-alkyloxazolines **4** to form the fused ring products **14** (Table 1).

Addition of the first acid chloride forms thiazolinium or oxazolinium salts **5** and **6**, respectively. Proton removal by Et_3N then forms the key *N*-acyl cyclic ketene-N,X-acetal (X = S, O) intermediates **7** and **8** which are nucleophilic. They react intramolecularly with the second acid chloride function to generate zwitterions **9/10** and then salts **11/12**. A second proton removal by Et_3N then generates the corresponding substituted 2,3-dihydrothiazolo[3,2-*a*]pyridine-5,7-dione **13** or 2,3-dihydrooxazolo[3,2-*a*]pyridine-5,7-dione **14**. Three different α,α-disubstituted malonyl chlorides were each reacted with various 2-alkyloxazolines and 2-alkylthiazolines (Table 1). Excellent isolated yields of both **13** and **14** were achieved in all the fourteen reactions conducted.

The overall reactions are depicted in Table 1. These fused ring systems, **13** and **14**, are highly functionalized and each still retains an *N*-acyl cyclic ketene-N,X-acetal (X = O, S) function with a reduced nucleophilicity due to the carbonyl function conjugated to the carbon–carbon double bond. The 2-alkyloxazolines **4** and 2-alkylthiazolines **1** were made by known methods[14–16] as shown in Scheme 3. We have reported the synthesis and characterization of each 2-alkylthiazoline used here.[13] The use of diacid chlorides containing α-protons did not lead to successful cyclizations. These α-protons are acidic and side reactions occur in the presence of Et_3N, instead of acyl substitutions (Scheme 1) observed with α,α-disubstituted malonyl chloride.

To expand the scope of this reaction, *N*-(chlorocarbonyl) isocyanate was used as the dielectrophile in place of α,α-disubstituted diacid chlorides. An analogous cyclization was expected based on a mechanism similar

Keywords: 2-Alkylthiazolines; 2-Alkyloxazolines; *N*-(chlorocarbonyl) isocyanate; Diacid chlorides; Ketene acetal.
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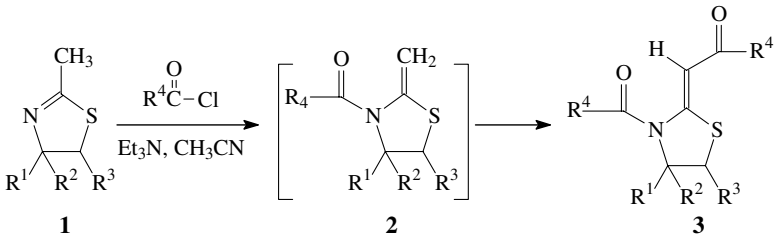
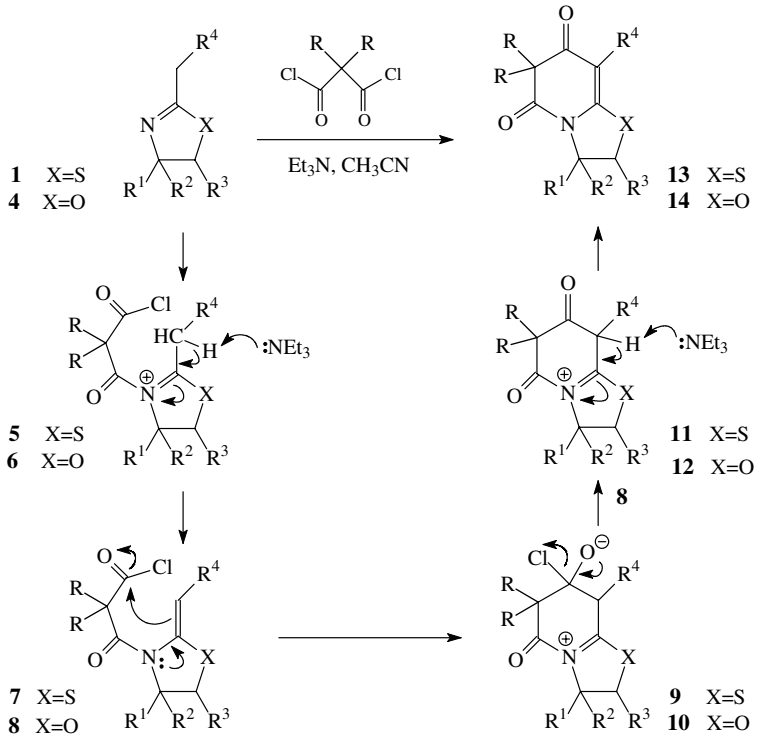
doi:10.1016/j.tetlet.2005.01.146



Scheme 1. Reaction of 2-methylthiazolines with 2 equiv of acid chloride.



Scheme 2. Proposed mechanism for reactions of 2-alkyloxazolines and 2-alkylthiazolines with diacid chlorides.

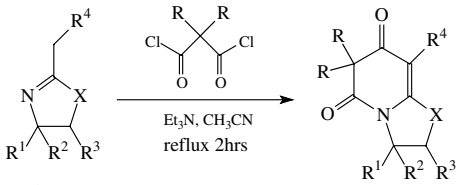
to that in Scheme 2. After reaction of the ring nitrogen with the acid chloride, proton removal by Et_3N generated *N*-acyl cyclic ketene-N,X-acetal (X = O, S) intermediates **15** or **16** (Table 2). We expected these species would be nucleophilic enough to react with the isocyanate carbon to form a six-membered ring. Indeed, experiments demonstrated these cyclizations occurred in excellent isolated yields (Table 2). The isolated 2,3-dihydrothiazolo[3,2-*c*]pyrimidine-5,7-diones **17** and 2,3-dihydrooxazolo[3,2-*c*]pyrimidine-5,7-diones **18** still contain a reactive ketene-N,X-acetal function generated by proton transfer from C-8 to N-6 after ketene acetal nucleophilic attack at the isocyanate carbon.

The use of *N*-(chlorocarbonyl) isocyanate to prepare **17** and **18** suggests that the analogous reactions on 2-alkylthiazolines, with exocyclic electron withdrawing groups, could generate the corresponding thiazolo- [3,2-*c*]pyrimidine-5,7-diones. This type of cyclization has been reported on 2-cyanomethylbenzothiazole in triethylamine/dioxane at ambient temperature.[17] We are currently exploring the applications on thiazoles without electron-withdrawing substituents on the 2-alkyl group.

Oxalyl chloride and phthaloyl dichloride (no α protons) did not undergo analogous cyclizations with 2-alkylthiazolines or 2-alkyloxazolines to generate the corresponding 5/5 or 7/5 ring fusions (Scheme 4). Similarly, phosgene failed to convert 2-alkyloxazolines or 2-alkylthiazolines to their corresponding 4/5 ring-fusion products (Scheme 4). The failure of oxalyl chloride to generate **20** was disappointing in view of the successful cyclization of oxalyl chloride on a 2-carbethoxythiazoline derivative reported by Shane et al. at room temperature in CH_2Cl_2.[18] Oxalyl chloride reacted extremely fast and exothermically with **1** in THF, acetonitrile, and CH_2Cl_2 generating black solutions and black residues. The use of dropwise additions at 0 °C or 23 °C failed to produce **20**. An electron-withdrawing R^4 function on **1** may play a crucial role in this reaction Scheme 4.

The facile synthesis of **17** reported here is of special interest due to the known important biological activities of some of these derivatives.[19] 2,3-Dihydrothiazolo[3,2-*a*]pyridine-5,7-diones generate pronounced increases of HDL cholesterol and marked decreases of LDL and VLDL cholesterol when administered to rats (in vivo).

Table 1. Reaction of 2-alkyloxazolines and 2-alkylthiazolines with α,α-disubstituted diacid chlorides

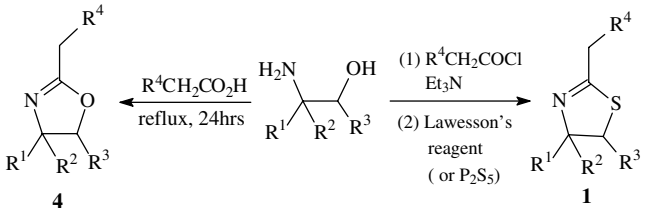


1 X = S
4 X = O

13 X = S
14 X = O

Entry	Substituents in **1** or **4**				X	R in ClOC–CR_2–OCl	Product	Yield (%)
	R^1	R^2	R^3	R^4				
1	H	H	H	H	S	CH_3	**13a**	94
2	H	H	CH_3	H	S	CH_3	**13b**	92
3	H	H	CH_3	CH_3	S	CH_3	**13c**	92
4	H	H	H	H	S	Et	**13d**	91
5	H	H	H	CH_3	S	Et	**13e**	90
6	H	H	H	H	S	$–CH_2CH_2CH_2–$	**13f**	91
7	H	H	H	CH_3	S	$–CH_2CH_2CH_2–$	**13g**	93
8	H	H	H	H	O	CH_3	**14a**	95
9	H	H	H	CH_3	O	CH_3	**14b**	94
10	H	H	H	H	O	Et	**14c**	92
11	H	H	H	CH_3	O	Et	**14d**	90
12	H	H	H	H	O	$–CH_2CH_2CH_2–$	**14e**	92
13	H	H	H	CH_3	O	$–CH_2CH_2CH_2–$	**14f**	92
14	CH_3	CH_3	H	H	O	$–CH_2CH_2CH_2–$	**14g**	89

The ratio of **1** or **4**/diacid chloride/Et_3N = 1:1:2.2. All yields are isolated yields.



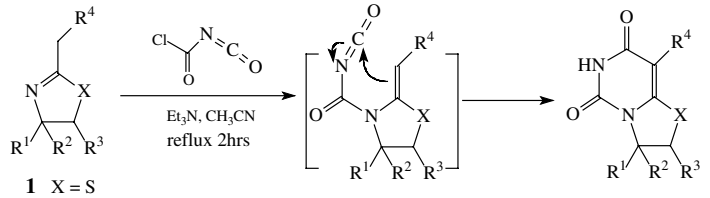
4 **1**

Scheme 3. Synthesis of 2-alkylthiazolines and 2-alkyloxazolines.

In summary, we have successfully demonstrated cyclization reactions of 2-alkyloxazolines and 2-alkylthiazolines with both diacid chlorides and *N*-(chlorocarbonyl) isocyanate. These reactions generate highly functional compounds and should have applications in molecular library formation by combinatorial syntheses. All of these cyclizations proceed readily under mild conditions, providing excellent isolated yields as shown by the example preparations given in Ref. 20. Further synthetic applications of these reactions are currently being investigated.

The detailed synthetic and isolation procedures and the full spectral identification of all compounds are

Table 2. Preparation of 2,3-dihydrothiazolo[3,2-*c*]pyrimidine-5,7-diones **17** and 2,3-dihydrooxazolo[3,2-*c*]pyrimidine-5,7-diones **18**



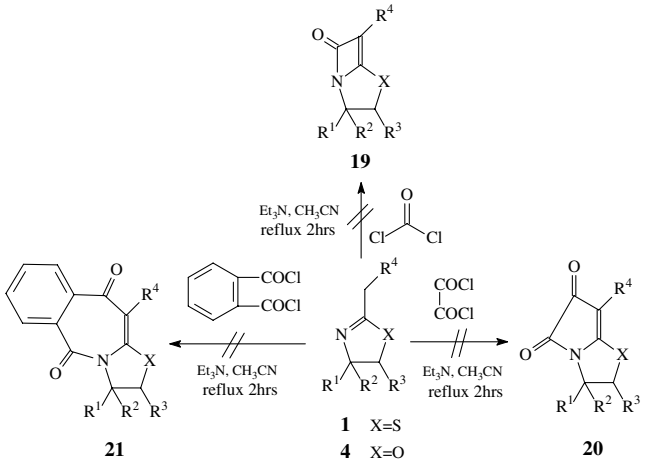
1 X = S
4 X = O

15 X = S
16 X = O

17 X = S
18 X = O

Entry	Substituents in **1** or **4**				X	Product	Yield (%)
	R^1	R^2	R^3	R^4			
1	H	H	H	CH_3	S	**17a**	94
2	H	H	CH_3	CH_3	S	**17b**	92
3	CH_3	CH_3	H	H	S	**17c**	92
4	H	H	H	CH_3	O	**18a**	90
5	CH_3	CH_3	H	H	O	**18b**	86

The ratio of **1** or **4**/*N*-(chlorocarbonyl) isocyanate/Et_3N = 1:1:2.2. All yields are isolated yields.



Scheme 4. Reaction of 2-alkylthiazolines and 2-alkyloxazolines with oxylal chloride, phthaloyl chloride, and phosgene.

provided in the supplementary data. The supplementary data is available online with the paper in ScienceDirect.

Acknowledgements

Partial support of this work by the National Science Foundation, Grant No. EPS 012618 and by Mississippi State University is acknowledged. Dr. E. A. Alley is thanked for obtaining the mass spectra in the supplementary data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.146.

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20. (a) Preparations of 6,6-dimethyl-2,3-dihydrothiazolo[3,2-*a*]pyridine-5,7-dione (**13a**): Dimethylmalonyl chloride (0.10 g, 0.59 mmol) was added dropwise to a stirred solution of 2-methylthiazoline **1** (51 mg, 0.59 mmol) and triethylamine (131 mg, 1.30 mmol) in acetonitrile 40 mL at room temperature. Then this solution was refluxed for 3 h and the solvent was removed by rotary evaporation. Water was added to the residue followed by extraction with dichloromethane (3 × 20 mL). The organic layer was washed with 10% aqueous sodium bicarbonate, brine, and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (silica gel, 1:1, hexane/ethyl acetate) to give **13a** (109 mg, 94%). (b) Preparation of 8-methyl-2,3-dihydrooxazolo[3,2-*c*]pyrimidine-5,7-dione (**18a**): *N*-(Chlorocarbonyl) isocyanate (0.22 g, 2.1 mmol) was added dropwise to a stirred solution of 2-ethyloxazoline (0.21 g, 2.1 mmol) and triethylamine (464 mg, 4.62 mmol) in THF 20 mL at room temperature. Then this solution was refluxed for 2 h and the solvent was removed by rotary evaporation. Water was added to the residue followed by extraction with dichloromethane (3 × 20 mL). The organic layer was washed with 10% aqueous sodium bicarbonate, brine, and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (silica gel, 1:1, hexane/ethyl acetate) to give **18a** (0.39 g, 90%).